American
Clinical Laboratory
Association

Statement

Of

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For

U.S. House of Representatives
Energy and Commerce Committee

Subcommittee on Health

Hearing on

21st Century Cures: Examining the Regulation of Laboratory-Developed Tests

September 9, 2014
9:30 a.m.
2322 Rayburn House Office Building

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Introduction

Chairman Pitts, Ranking Member Pallone, and members of the Subcommittee, the American Clinical Laboratory Association (ACLA) is pleased to have this opportunity to testify at today's hearing, "21st Century Cures: Examining the Regulation of Laboratory- Developed Tests."

ACLA is a not-for-profit association representing the nation's leading providers of clinical laboratory services, including local, regional, and national laboratories. Our diverse membership represents a broad array of clinical laboratories, includes large national independent labs, reference labs, esoteric labs, hospital labs, and nursing home laboratories. ACLA members are actively engaged in the creation and performance of innovative and much-needed Laboratory-Developed Tests (LDTs) that have helped to transform the standard of clinical care in this country and provide great hope for further improvements in the future.

ACLA and its member laboratories are committed to developing and providing safe, reliable, and clinically-meaningful diagnostic testing services to patients and ensuring adequate and appropriate regulatory oversight of the tests they perform. We do appreciate the willingness of the FDA to engage in a dialogue with our organization regarding its proposal, and the Agency has reached out to us. ACLA and its member laboratories are in the process of analyzing the documents released on July 31, 2014, and we fully intend to provide detailed and thoughtful comments on the documents once they are formally released as draft guidance. However, ACLA and the FDA fundamentally disagree on several key issues, including their statutory authority to regulate LDTs and the promulgation of new regulatory oversight through guidance documents,

and ACLA has other concerns related to the framework as outlined in the Congressional notification documents, all of which will be addressed in the following written statement.

In our testimony, we wish to highlight the following areas:

- The vital role and value of diagnostics and Laboratory-Developed Tests in clinical care;
- The current regulatory framework governing Laboratory-Developed Tests;
- The lack of statutory authority for the FDA to regulate Laboratory-Developed Tests;
- The FDA's Claim of jurisdiction over LDTs and its policy of "enforcement discretion" are relatively recent;
- The inappropriateness of the guidance process for regulating LDTs;
- Questions and concerns with FDA proposed framework;
- FDA's inadequate resources to handle the increased workflow;
- FDA regulation could severely affect patient access to cutting-edge diagnostics; and
- Effective modernization of current regulatory oversight to address new technologies and advancements

The Vital Role of Diagnostics, and LDTs, in Clinical Care

Laboratory-Developed Tests (LDTs) are tests that laboratories develop and validate in their own laboratories and that are not sold as kits to other laboratories or to other facilities. LDTs also include tests where laboratories modify an existing FDA-approved or FDA-cleared kit and then validate the modified test internally. LDTs are an extremely common part of laboratory medicine. Laboratory-Developed Tests are the backbone of clinical care in the United States.

The diagnostic information they yield empowers patients and their doctors with the tools they need to best manage patient care.

A large proportion of the clinical laboratory tests performed in this country are performed as LDTs, from routine tests such as pap smears and complete blood counts, to the most cutting-edge molecular and genetic tests in cancer, heart disease, and rare and infectious diseases. These are tests developed by physicians, scientists and other highly-trained personnel working in a single laboratory, according to its own processes, to furnish a diagnostic result for use by a clinician. These tests most often are created in response to an unmet clinical need, or where the existing diagnostic tests are insufficient or fail to incorporate the latest in scientific and medical research. Nearly all FDA-approved and FDA-cleared test kits begin as LDTs, and, in many cases, LDTs represent the standard of care.

Through the innovations in clinical laboratories, we are diagnosing and characterizing diseases earlier and more precisely than ever before imagined – whether for diabetes, infectious disease, cancers, and rare diseases. With these powerful diagnostic tools, patients have access to more targeted therapies sooner, which inevitably lowers costs, increases the quality of care, and saves lives.

Current Regulatory Framework Governing Laboratory-Developed Tests

The clinical laboratory industry has been extensively regulated for decades under a comprehensive, interlocking framework of federal laws, state laws, and peer review "deemed" authorities. The primary federal law governing labs has been the Clinical Laboratory Improvement Amendments (or CLIA), specifically the Clinical Laboratory Improvement

Amendments of 1988.[1] CLIA creates stringent requirements governing the operation of clinical laboratories to ensure the safe and accurate function of laboratories and the testing services they provide. These requirements cover the laboratories themselves, the necessary certifications for laboratory personnel from pathologists and geneticists to technicians, and the documentation of procedures for individual clinical laboratory tests. In addition, laboratories also are subject to inspections under both CLIA and state law. Further, moderate and highly complex laboratories, including all ACLA members, can choose to submit to additional oversight through deemed peer review authorities, such as the College of American Pathologists, the Joint Commission, and others, which add additional expertise in reviewing both the operation of the laboratory and the analytical and clinical validity of individual tests. This additional oversight for moderate and high complexity laboratories also involves the use of proficiency testing to ensure the accuracy of testing results. A group of 23 lab directors from the nation's leading academic medical centers wrote to the Acting Director of the Office of Management and Budget on July 16, 2014 and stated that "as part of this oversight, clinical laboratory physicians and scientists, including most of the signatories to [the] letter, perform careful inspections of laboratory facilities, exhaustive review of test protocols and validation, and continually monitor laboratory performance. This regulatory framework requires both extensive validation and continuous monitoring to ensure the performance, quality, and reliability of diagnostic services, yet allows laboratories the flexibility to develop and validate lab tests quickly and, thus, more quickly adopt new scientific knowledge and rapidly respond to unmet public health needs."[2]

[1] Pub. L. 100-578.

[2] http://www.aruplab.com/AboutARUP/PressRoom/PressRelease/2014/Letter-to-OMB-from-Lab-Leaders.pdf

Operating under this comprehensive yet flexible LDT oversight framework, the field of laboratory medicine has thrived, producing some of the most spectacular advances in medicine to occur in the last century. As highlighted in the aforementioned academic medical center lab director letter to OMB, "LDTs have long addressed emerging public health risks, such as HIV. For example, no HIV-1 antibodies confirmatory test was available when the HIV-1 screening test was introduced in 1985. Clinical laboratories developed and validated an LDT Western blot to meet the critical need to establish definitive diagnoses of HIV-1. It took two years before an FDA-approved Western blot test became available. Even now, the FDA-approved Western blot kit has not significantly changed since its first approval. Because obtaining additional FDA approvals for test kit modifications would be so burdensome, the manufacturer has not modified the test to keep up to date with the medical science."[3] Advances such as these "came about because of, and would not have been possible without, the current regulatory framework governing LDTs."[4]

LDTs have transformed clinical practice and dramatically altered treatment guidelines, as illustrated by the impact of Onco*type* Dx, a genomic LDT shown to predict whether chemotherapy is likely to benefit women with early-stage invasive breast cancer. Whereas 50 years ago, all women with breast cancer were referred for intensely toxic and debilitating chemotherapy treatments, we now know that only about 4 in 100 women diagnosed with early-stage breast cancer actually receive benefit from chemotherapy.[5] In the last ten years, the

[3] http://www.aruplab.com/AboutARUP/PressRoom/PressRelease/2014/Letter-to-OMB-from-Lab-Leaders.pdf

[4] *Id.*

[5] Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006; 24(23): 3726-34.

Onco*type* Dx breast cancer test has helped over a hundred thousand patients around the world avoid chemotherapy and its side effects while saving the healthcare system an estimated more than $2.5 billion in treatment costs.

FDA Lacks the Statutory Authority to Regulate Laboratory-Developed Tests

As detailed in the Citizen Petition filed by ACLA last year, ACLA strongly believes that the FDA cannot regulate LDTs, through guidance or otherwise, because the Agency lacks the requisite statutory authority to regulate these vital diagnostic services.[6] FDA lacks the jurisdiction to regulate LDTs for several reasons.

LDTs are not "devices" as defined in the Food, Drug and Cosmetics Act (FDCA).[7] As the text and legislative history of the "device" definition show, this term encompasses only articles. LDTs are proprietary procedures for performing a diagnostic test using reagents and laboratory equipment. They are essentially know-how, not physical articles. Therefore, they are not subject to regulation under the FDCA.

Additionally, FDA's assertion of jurisdiction over LDTs is incompatible with the 1988 Amendment to the CLIA program (CLIA '88) and its legislative history. In amending CLIA, Congress explained its intent to regulate laboratory testing under a single statute: the amended CLIA. To that end, Congress created a comprehensive statutory framework for precisely the services that FDA now seeks to regulate under the device authorities of the FDCA. Congress

[6] ACLA Citizen Petition, Docket No. FDA-2013-P-0667 (Jun. 4, 2013), *available at* http://www.acla.com/wp-content/uploads/2013/12/060413-Citizen-Petition-to-FDA-Regarding-Laboratory-Developed-Tests-LDTs.pdf.

[7] 75 Fed. Reg. 34463 , 34463 (June 17, 2010).

made no mention of FDA having any authority to regulate LDTs under the previously enacted "device" definition.

Lastly, LDTs do not present an essential prerequisite for FDA jurisdiction under the FDCA: commercial distribution. FDA has defined "commercial distribution" in various contexts to require that a product be delivered, distributed, or placed on the market. LDTs are created and performed in a single laboratory, not manufactured and distributed. As non-tangible know-how and testing services at clinical laboratories, LDTs do not meet any of these conditions.[8]

The FDA's Claim of Jurisdiction over LDTs and its Policy of "Enforcement Discretion" are Relatively Recent

The FDA says that Congress gave the agency statutory authority to regulate LDTs nearly forty years ago when Congress passed the Medical Device Amendments of 1976 (MDA). The agency said that, since that time, it has opted to "exercise enforcement discretion" until now. That claim is contradicted by a review of actions and statements by Congress and the FDA throughout the years. It was not until twenty years after passage of the Medical Device Amendments that the FDA publicly stated that it could – but chose not to – regulate LDTs.

The legislative history of the Medical Device Amendments of 1976 contains no statement by the FDA or documentation submitted by the FDA to Congress that the agency considered LDTs to be "devices" under the framework of the MDA. Indeed, the legislative history shows that Congress itself believed that "devices" are tangible products and articles, but not processes such

[8] ACLA Citizen Petition at 2.

as LDTs.[9] Subsequent to passage of the MDA, when the agency undertook the rulemaking process and established advisory committees to classify all known devices, it did not mention then-existing LDTs as being "devices" subject to classification and regulation. If, in fact, the FDA thought at that time that LDTs were "devices" that it had the authority to regulate, then one would expect that the FDA would have explained to stakeholders why it was declining to classify them for regulation, but it did no such thing.

In 1988, Congress passed the Clinical Laboratory Improvement Amendments, which established a comprehensive statutory and regulatory framework for oversight of all clinical laboratory testing on humans in the United States. During the time that Congress was debating the legislation, the FDA stood by in silence, never once claiming that it had jurisdiction over any clinical laboratory tests developed in-house. The CLIA regulations that were finalized in 1992 did not include a regulatory role for the FDA with respect to LDTs or any other lab processes, and we are not aware that the FDA sought to assert such a role at the time.

The first time that the FDA made a public claim about its authority to regulate LDTs as devices was in a draft guidance document in 1992.[10] Stakeholders objected, and the FDA removed any reference to LDTs in the final guidance, released in 1996.[11]

It was not until 1996 – two decades after the Medical Device Amendments – when the FDA claimed in a statement in an official publication, the Federal Register, that it had jurisdiction

[9] S. Rep. No. 94-33, 94th Cong., 1st Sess. at 17 (Mar. 11, 1975).

[10] Draft Compliance Policy Guidance: Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation (undated) at 4.

[11] *See* FDA, Compliance Policy Guide 7124.32, Commercialization of In Vitro Diagnostic Devices (IVDs) Labeled for Research Use Only and Investigational Use Only (May 1996).

over LDTs but that it was not exercising its authority to regulate them. It hinted at its jurisdictional authority and its exercise of enforcement discretion, stating that although it had not "actively regulated" LDTs, it might do so in the future.[12] At the time, ACLA and other stakeholders filed comments challenging the FDA's assertion that it had the authority to oversee LDTs for twenty years but simply never used that authority. In 1998, in its denial of a citizen petition on LDTs, the FDA again stated that it "may regulate assays developed by clinical reference laboratories strictly for in-house use as medical devices."[13] This assertion has been repeated in the years since then, although it was not until recently that FDA determined that it would use its purported enforcement authority for the first time.

The Inappropriateness of the Guidance Process for Regulating LDTs

The FDA takes the position that it has the jurisdiction to regulate LDTs but has always chosen to exercise its regulatory discretion with regard to those tests. The clearest statement of that discretion is found in the FDA's announcement of the Final Rule regulating Analyte Specific Reagents, which are the component of many LDTs. In promulgating the ASR Rule, the FDA declined to classify Laboratory-Developed Tests as Class II or III medical devices because, as the agency stated, "FDA recognizes that the use of in-house developed tests has contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes

[12] Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 61 Fed. Reg. 10484 (Mar. 14, 1996).

[13] FDA Response to Hyman Phelps & McNamara, P.C., Citizen Petition, Docket No. 92P-0405 (Aug. 12, 1998).

in this area could have negative effects on the public health."[14] In announcing a change to that policy, FDA cannot proceed simply through the issuance of guidance documents.

First, given that the original announcement of this policy was as part of a notice and comment rulemaking, the reversal of the policy—which FDA is asserting here—must be done in the same way. Because FDA set forth its policy regarding Laboratory-Developed Tests in the Federal Register, pursuant to notice-and-comment procedures, if the agency is going to change its policy, then it must follow that same notice-and-comment procedure.[15]

There is little question that by its actions, FDA is expanding its current regulations to an entirely new industry. The FDA cannot newly regulate an entire industry sector merely by issuing a few guidance documents. Federal courts long have held that when a guidance document significantly broadens the application of a regulation or set of regulations, it is invalid without actual notice-and-comment rulemaking.[16] It is also well-established that an agency cannot sidestep notice-and-comment rulemaking requirements by claiming that a major legal addition to a rule is merely an interpretation of an existing obligation.[17] Here, if the FDA's guidance is in any way similar to the documents the FDA shared with Congress in July, it would expand the application of existing regulations that currently are not applicable to laboratories offering LDTs. In some cases, the guidance would completely contradict what is in current regulation, which in itself would require notice-and-comment rulemaking. Expansion of the FDA's regulatory regime to

[14] 62 Fed Reg. 62243, 62249 (Nov. 21, 1997).

[15] *See, e.g., Ball Memorial Hospital v. Leavitt,* 2006 WL 2714920 (D.D.C. 2006).

[16] *See, e.g., Appalachian Power Co. v. EPA*, 208 F.3d 1015 (D.C. Cir. 2000).

[17] *See Paralyzed Veterans of America v. D.C. Arena L.P.*, 117 F.3d 579 (D.C. Cir. 1997).

LDTs significantly broadens the scope of current regulations to an entire industry, and it would be far more than an interpretation of an existing obligation on labs. Therefore, according to years and years of federal court rulings, the FDA cannot regulate LDTs through subregulatory guidance documents alone.

Furthermore, the FDA cannot claim, as it often does with regard to guidances, that these documents "do not establish legally enforceable responsibilities" and that they merely "describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited." It includes such language in all of its guidance documents, including those it shared with Congress in July. But, if finalized, the LDT guidance documents most certainly would impose legally enforceable responsibilities on labs, and they contain far more than just "recommendations." The documents we have seen are packed with citations to specific existing statutory and regulatory provisions and very direct statements that LDTs for the first time would be subject to those provisions. As an example, the FDA states that any lab that fails to follow certain other requirements in the document "will have opted to not be within the scope" of the FDA's current policy under which labs do not have to register and list their tests.[18] If device registration and listing is not a "legally enforceable responsibility" that suddenly would be imposed on labs, then it is hard to see what would be. There are many other examples of legally enforceable responsibilities on virtually every page of the documents the FDA shared with Congress that completely contradict the agency's claim that the guidance is just describing its current thinking and making recommendations.

[18] Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories, Framework for Regulatory Oversight of Laboratory-Developed Tests (LDTs) at 17.

Moreover, though the Agency stated that in its July 31, 2014 response to the ACLA Citizen Petition [attached] that "any such guidance would not establish any legal obligations" under the theory that the legal obligations arise under the FDCA itself, this is plainly not true.[19] As summarized to Congress, the final guidance would clearly obligate laboratories, under threat of enforcement action to newly comply with FDA regulations and guidances. Some of these obligations are the same as seen by device manufacturers, but others are completely novel and not grounded in any statute or regulation.[20]

The difference between proceeding through guidance and proceeding through regulation is not merely an academic one. The FDA's "Good Guidance Practices" do not extend the same rights and protections to all stakeholders that notice-and-comment rulemaking would.[21] There are key differences in the obligations imposed upon the FDA – or any federal agency – when engaging in rulemaking, versus the requirements the FDA follows with respect to guidance. Although the FDA plans to accept public comment on the draft guidance, unlike notice-and-comment rulemaking, the FDA is not required to respond to stakeholder comments and explain its rationale for amending draft guidance – or not.[22] This is critically important to understanding the "agency's current thinking." The FDA is also not required to conduct any burden analysis or regulatory impact analysis when it issues guidance, both of which are standard features of notice-and-comment rulemaking. If the agency did proceed through notice-and-comment rulemaking, there is no doubt

[19] FDA Response to ACLA Citizen Petition, Docket No. FDA-2013-P-0667 (Jul. 31, 2014).at 15.

[20] *See*, e.g., Anticipated Details of the Draft Guidance at 16. The FDA plans to require laboratories to submit "notification" of basic information about LDTs to the Agency, yet no such framework exists in statute or regulations for other "device" manufacturers.

[21] Food and Drug Administration Modernization Act of 1997, Pub. L. 105-115 (1997), § 405; 65 Fed. Reg. 56468 (Sept. 19, 2000).

[22] *See* 21 C.F.R. § 10.115(g)(iv).

that it would have to put the public on notice that its plans to start regulating an entire industry sector are likely to have a major impact on the entire laboratory industry.

ACLA strongly opposes the claim that the FDA has the authority to regulate Laboratory-Developed Tests. However, if the agency nevertheless moves forward in its attempt to regulate LDTs, it most certainly cannot do so merely through guidance documents. It must use notice-and-comment rulemaking to vastly expand the application of existing regulation and to amend those regulations that do not apply to LDTs or that contradict its plans for regulating LDTs.

FDA's Guidance Documents Raise Real Concerns Due to Unanswered Questions

The documents released by the Agency on July 31, 2014 go far beyond reflecting current Agency thinking, as they propose an entirely new regulatory framework that will be applied to clinical laboratories developing LDTs for the first time. If the FDA were to finalize this guidance, it would represent nothing short of a wholesale reimagining of the regulation of laboratories, subjecting laboratories to an entirely new set of requirements that they have never faced before.

The Agency has put forth a high-level, conceptual vision of how it would regulate LDTs, while providing very little concrete guidance to the laboratories as to what specifically the FDA will require and how to devise a compliance strategy or operationalize the requirements.

Interplay of FDA Requirements with Existing LDT Oversight Under CLIA

There is no discussion of how any additional regulation by the FDA would interact with the regulation already in place under the CLIA program, including those functions performed by deemed authorities. There are many areas of commonality and overlap, specifically with respect to validation, inspections, and quality systems regulation, and yet there is no discussion of how

two separate regulatory authorities would regulate the laboratory industry in a way that would not impede innovation. The Agency had discussed a third guidance document that it planned to release with the actual draft guidance, a document which was to specifically address how the Quality Systems Regulation (QSR) requirements applicable to devices under the FDA would interplay with the quality requirements under CLIA.[23] The Agency has stated that it no longer plans to release such a document with the actual guidance documents. Rather, it has said it will rely on a third-party organization to explain how CLIA and FDA's QSR requirements can be reconciled. ACLA believes it is wholly inappropriate for FDA to leave such a vital issue to an unaccountable third party to resolve.

What Is the "Device" to be Regulated, and Where Does "Manufacture" Take Place vs. Test Performance

The documents released by the FDA fail to address the fundamental differences between device manufacturers and clinical laboratories. Unlike manufacturers of IVD test kits, laboratories are both the innovators and providers of clinical laboratory services, utilizing their advanced knowledge, training, and education in the practice of laboratory medicine to deliver the highest quality health care services for millions of real, every day patients. Knowing this, it would be unreasonable to deem a laboratory, "a manufacturer" and claim that there is a "level playing field," when manufacturers and laboratories run fundamentally different operations.

[23] *See, e.g.*, Minutes from Negotiation Meeting on MDUFA III Reauthorization: June 27, 2011, at 3, *available at* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm263026.htm.

Unlike a device manufacturer, which produces a test kit or device that then is sold to another entity that ultimately performs the test, a clinical laboratory is an integrated operation consisting of highly trained and certified personnel who design, validate, perform, and interpret laboratory tests to furnish test reports that then can be used by ordering physicians, in concert with other information, to make treatment decisions. Defining exactly what the "device" is that FDA seeks to regulate, or where the "manufacture" of the test ends and the performance of the test begins, has yet to be explained.

What are "High Risk" and "Moderate Risk" LDTs?

Under the proposed regulatory framework described in the documents released on July 31, 2014, the FDA will not issue draft guidance describing the risk classification of LDTs for 18 months after the finalization of the guidance, with final guidance on risk classification not being issued for two years after the finalization of the guidance. The Agency and stakeholders have spent years attempting to define "high risk" and "moderate risk" in the context of clinical diagnostics, and it is crucial that the Agency clearly define such fundamental principles before instituting a new regulatory framework based on those definitions.

Defining "Adverse Events" and "Device Malfunctions" In the Context of LDTs

It is unclear in the context of LDTs what constitutes an "adverse event" that must be reported by a laboratory. For example, how precisely would a laboratory test contribute to the death of, or serious injury to, a patient? Would the FDA consider it an "adverse event" if a patient's cancer returned after an LDT test predicted a 90 percent chance that cancer would not return? Even if "adverse events" were defined in a way that applied in the diagnostic context, it is not clear from an operational standpoint how laboratories could be expected to report adverse

events. Referring physicians use LDT test results as one part of a broader clinical picture to make treatment decisions for patients, and these clinical decisions and patient encounters often occur outside the laboratories' knowledge or involvement. Thus, laboratories would not have access to information on a patient's other clinical inputs or prognosis after the test results are reported to referring physicians.

Similarly, it is unclear in the context of LDTs what constitutes a "device malfunction" that the LDT "manufacturer" would be required to report to the FDA under 21 C.F.R. § 830.50(a). This issue arises in part because the FDA is seeking to regulate a service rather than a product, and in part because of the FDA's expansive view of the test system as including, for example, patient demographics, sample procurement and preparation, and reporting. Would an error in patient demographic data entry constitute a "device malfunction" if it had no effect on the test result? What if a momentary interruption in result reporting were to occur due to information system technical difficulties, but the problem was promptly resolved without significantly affecting the timeliness of result delivery? If broadly interpreted and enforced, the requirement to report "device malfunctions" could overwhelm laboratories with reporting incidents that have no adverse effect on the test results or patient care.

Modifications to FDA-Approved and Cleared Tests

High complexity clinical laboratories frequently purchase FDA-approved or FDA-cleared test kits from device manufacturers and modify these test kits, thereby creating LDTs, to improve the performance of the diagnostics, address problems or issues with the FDA-approved or cleared devices, or to incorporate the latest research and clinical knowledge. For instance, a well-known FDA-approved ALK gene FISH test kit, an *in vitro* companion diagnostic used to

aid in treatment selection for patients with Non-Small Cell Lung Cancer, was found by one lab to suffer from poor assay performance. These tests, as LDTs, current are regulated by CLIA and undergo the necessary validations as outlined earlier in this document.

The Agency has stated in the framework documents released to Congress on July 31, 2014 that any modifications to "an FDA cleared/approved device in a way that affects device performance or intended use is considered to be a device manufacturer… [and] [t]hese modified devices must meet premarket submission requirements."[24] To force a laboratory to undergo such a burdensome and expensive premarket review process in order to make modifications to an FDA-approved or cleared test kit is unreasonable, an encroachment on the practice of medicine, and will be a disincentive for laboratories that otherwise would make such changes to improve diagnostic capabilities of FDA-approved or FDA-cleared tests, which will negatively impact patient access to cutting edge diagnostics.

Are anatomic pathology services considered LDTs subject to FDA regulation?

The anticipated details of this draft guidance leave unclear the regulatory status of many anatomic pathology services provided by laboratories. Anatomic pathology services typically involve the preparation of a biopsy or cellular specimen on a slide (the "technical component") for microscopic examination and interpretation by a pathologist (the "professional component"). Examples of such services include histopathology or surgical pathology, cytopathology (including the Pap smear test), and hematology. These procedures may include FDA-approved or -cleared components and instruments, components that are exempt from FDA premarket

[24] Anticipated Details of the Draft Guidance at 26.

review, or modifications of FDA-approved, -cleared or -exempt components or instruments, and are often performed in laboratories that are independent of health care facility laboratories.

It is difficult to see how the FDA could consider a pathologist reviewing a slide as an *in vitro* diagnostic or an LDT; in this instance, the pathologist is practicing his or her field of medicine just as any other physician when practicing medicine in his or her office. However, the Agency has written the anticipated details of the draft guidance so broadly that they appear to sweep into the risk-based framework any procedure a laboratory performs that is intended for clinical use and is not an unmodified FDA-approved or -cleared test kit, unless specifically excepted. Under what circumstances, if any, would the FDA view the technical component, the professional component, or the technical and professional components of anatomic pathology together, as a "test system" constituting an LDT subject to the risk-based framework?

FDA Lacks the Resources to Handle the Increased Workflow

We also have very real concerns about resource constraints within the Agency to effectively manage this entirely new area of diagnostic regulation. There are tens of thousands of LDTs in existence today, with hundreds of new tests created every year.

According to CMS, of the 36,432 non-waived laboratories regulated under CLIA, 11,633 CLIA certified laboratories perform at least one or more specialties categorized as high-complexity, which is the only category of labs that are permitted to perform LDTs. A majority of these 11,633 laboratories develop and perform LDTs, many of which could be classified as moderate- or high-risk, depending upon how FDA tailors the risk classifications two years after the finalization of the framework guidance.

In 2013, the FDA approved 23 pre-market approval applications.[25] The Agency has stated in calls with industry stakeholders that it anticipates that the initial set of submissions for the "highest risk" LDTs will be around 100 tests, a number we believe falls far short of the actual number. This is an incredible workload for any agency or organization to undertake, and ACLA has serious concerns about the FDA's ability to handle this additional workload.

FDA Regulation Could Severely Affect Patient Access to Cutting-Edge Diagnostics

Subjecting LDTs to FDA regulation would eliminate the very characteristics which makes LDTs and the regulatory framework that presently govern them so vital: flexibility and nimbleness in their ability to respond to unmet needs. The flexibility afforded under the CLIA regulatory framework allows laboratories to develop tests quickly and to update them regularly as research and medicine advances, giving patients access to the most current diagnostic testing available. Such flexibility would be lost under the FDA device regulatory framework.

Additionally, FDA regulation of LDTs as medical devices would dramatically slow not only the initial premarket approval of new tests, but also improvements to existing tests, delaying access to new and improved diagnostic testing services for patients and clinicians. Under the current CLIA regulatory framework, laboratories may continually modify and update their tests to reflect medical research advances, provided that the laboratory appropriate validate and document test modifications. Under the FDA device regulatory framework, and as outlined in the proposed LDT framework provided to Congress on July 31, 2014, these modifications would

[25] *See, e.g.* *http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/ucm344734.htm*.

require supplemental filings and authorizations from the FDA.[26] These additional authorizations can take months to obtain, and in many cases, laboratories could not implement the modifications in the interim. Therefore, FDA regulation would impede scientific progress in clinical diagnostics.

ACLA Has Supported Modernization of Current Regulatory Oversight to Address New Technologies and Advancements

As ACLA stated in its June 2013 Citizen Petition to the FDA, "The CLIA framework has worked very well. Over the past few decades, health care providers have ordered millions of LDTs for their patients with few problems. With regard to genetic tests, for example, the Secretary's Advisory Committee on Genetics, Health, and Society has stated that 'there have been few documented cases in which patients experienced harm because of errors in a CLIA-regulated genetic test.'[27] Even though laboratories are not required to report adverse events, litigation or other publicity likely would have revealed more widespread incidence of harm if such harm had in fact occurred. Thus, regulation of LDTs under CLIA has effectively protected the public health.

To the extent that stakeholders have concerns about possible gaps in the clinical validation of LDTs, the most logical and appropriate solution would be to amend CLIA and/or its regulations. It would be overly burdensome to superimpose a new bureaucratic regime on the laboratory industry which is already highly regulated under CLIA. It also would be like trying to

[26] *See, e.g.*, FDCA § 515(d)(6), 21 C.F.R. §§ 807.81(a)(3), 814.39; Anticipated Details of the Draft Guidance.

[27] Secretary's Advisory Committee on Genetics, Health, and Society, "U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services" (Apr. 2008), at 32, *available at* http://oba.od.nih.gov/sacghs/sacghs_oversight)report.pdf.

fit a square peg into a round hole to impose an additional layer of regulation based on a statute designed for products (FDCA) rather than laboratory testing procedures."[28]

ACLA and its member laboratories have always been committed to ensuring patient access to accurate, reliable, and meaningful clinical laboratory tests that improve the quality of care, decrease costs, and improve the lives of patients. ACLA has long supported modernizing the regulatory requirements under the CLIA program to keep pace with changing technology. We are confident there are policies that can be developed to accomplish this without doubling or tripling the regulation, oversight and cost.

Conclusion

Chairman Pitts, Ranking Member Pallone, and members of the Subcommittee, thank you for this opportunity to testify today. ACLA is grateful for the opportunity to share our view on the regulation of Laboratory-Developed Tests. The Path to 21st Century Cures Initiative has shown that medical innovation in the U.S. has moved health care ahead by leaps and bounds and even more exciting innovations are just on the horizon. The Initiative has also shown that clinical laboratory diagnostics are a critical and powerful tool in this effort and will enable us to provide patients with higher quality health care at lower costs. To the extent that additional oversight of LDTs is necessary, we continue to believe that the best vehicle for that is modification of CLIA, which already extensively regulates LDTs. ACLA commends you for your leadership and looks forward to working with you, the FDA, and the Administration to

[28] ACLA Citizen Petition at 18.

ensure regulation of LDTs strikes the right balance between innovation, safety, and patient access.