

21ST CENTURY CURES: EXAMINING THE REGULATION OF LABORATORY-DEVELOPED TESTS

HEARING BEFORE THE SUBCOMMITTEE ON HEALTH OF THE COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES ONE HUNDRED THIRTEENTH CONGRESS

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¹ Dr. Shuren did not respond to questions for the record.

² The bill is available at <http://docs.house.gov/meetings/IF/IF14/20140909/102625/HHRG-113-IF14-20140909-SD009.pdf>.

21ST CENTURY CURES: EXAMINING THE REGULATION OF LABORATORY-DEVELOPED TESTS

TUESDAY, SEPTEMBER 9, 2014

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 9:32 a.m., in room 2322 of the Rayburn House Office Building, Hon. Joe Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Shimkus, Blackburn, Guthrie, Griffith, Bilirakis, Ellmers, Pallone, Schakowsky, Green, Barrow, and Waxman (ex officio).

Also present: Representative Eshoo.

Staff present: Clay Alspach, Chief Counsel, Health; Leighton Brown, Press Assistant; Noelle Clemente, Press Secretary; Sydne Harwick, Legislative Clerk; Robert Horne, Professional Staff Member, Health; Carly McWilliams, Professional Staff Member, Health; Tim Pataki, Professional Staff Member; Chris Sarley, Policy Coordinator, Environment and Economy; Heidi Stirrup, Health Policy Coordinator; John Stone, Counsel, Health; Ziky Ababiya, Democratic Staff Assistant; Phil Barnett, Democratic Staff Director; Eric Flamm, Democratic FDA Detailee; Debbie Letter, Democratic Staff Assistant; Karen Nelson, Democratic Deputy Committee Staff Director for Health; and Rachel Sher, Democratic Senior Counsel.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. The subcommittee will come to order. The chair will recognize himself for an opening statement.

Today's hearing is another in a series of 21st Century Cures hearings. Primarily focuses on FDA's July 31, 2014, notification to Congress that it intends to issue draft guidance on a framework for oversight of the laboratory-developed test, the LDTs. This notification was required by Section 1143 of the Food and Drug Administration's Safety and Innovation Act of 2012, and provides us with an opportunity to hear from the Agency about whether it has adequately answered the myriad of procedural and substantive questions that were the subject of much debate leading up to the passage of FDASIA.

It is indisputable that the draft guidance documents the Agency recently released would fundamentally alter the regulatory landscape for the review and oversight of LDTs and the clinical labs that develop them. That fact alone has raised legitimate concerns about whether FDA can or should use guidance to promulgate a new regulatory approach. It is also indisputable that innovative laboratories and health care providers develop and perform tests and procedures that advance personalized patient care. Because of the critical role they can play in the decisions patients make with their doctors, these tests, regardless of who develops or manufactures them, must be accurate and reliable. Any framework adopted must not only prioritize patient safety, which should always be paramount, but also encourage robust investment and allow for continued innovation. In order for that to happen, a company or venture capitalist that invests in the development, testing, and FDA review of a diagnostic product must have the certainty that labs will not copy it and promote their alternatives the next day. On the other hand, many innovative tests and procedures are developed in labs, including continuous, iterative improvements to FDA-approved products that often become the standard of care. Any regulatory approach must carefully address these complex issues.

Dr. Shuren has been a key voice throughout the 21st Century Cures Initiative, and I thank him for his willingness to come to the table yet again. The Committee invited CMS to testify on its roles and responsibilities administering the Clinical Laboratory Improvement Amendments regulations, which includes lab practices, certification, and personnel, but they were unable to do so.

We have a number of questions about FDA's proposed path forward, and I look forward to hearing from all of our witnesses on the second panel about its potential impact.

And with that, the chair yields back, and now recognize the Ranking Member, Mr. Pallone, for 5 minutes.

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

The Subcommittee will come to order.

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We have a number of questions about FDA's proposed path forward, and I look forward to hearing from all our witnesses on the second about its potential impact.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairman Pitts.

New technologies and advances in medicine can improve the quality of life for millions of Americans, but the use of these advances can also pose serious risks to individual patients if they are not clinically accurate. And this is why we have regulation, and it is why the FDA has proposed commonsense changes that merely bring safety regulations up-to-speed with medical progress.

Lab-developed tests have come a long way since Congress gave FDA the authority to regulate all in vitro diagnostic tests in 1976. Advances in science and technology have enabled labs to develop more sophisticated tests that allow physicians to identify genetic factors in diagnosing disease, and this has allowed for early detection and more targeted medical interventions.

Recently, genetic tests have identified specific gene sequences which can help doctors design an approach that patients are more likely to respond to. Identifying the HER2/neu gene in patients allowed oncologists to target this unique form of breast cancer with the drug Herceptin, instead of radiation, vastly improving patient outcomes. Similarly, the identification of mutations of the BRCA2 gene—or BRCA1 and BRCA2 genes—can tell doctors if a patient is at an increased risk for developing breast or ovarian cancer. Last year, the actress Angelina Jolie revealed that she learned she was carrying the BRCA1 gene and had an 87 percent risk of developing breast cancer. Armed with this information, the actress and her doctors took drastic action to prevent the likely onset of cancer later in life, and based on the results of this test, she took her future health into her own hands and obtained a preventative double mastectomy. And while the actress's actions have inspired considerable debate as to who should get tested, and to what extent they should undertake preventative measures, the fact remains that many of these tests, including those used in detecting the BRCA genes, never obtained FDA approval.

The consequences of information provided by tests like these is great, which is why in 2010 the Subcommittee on Oversight and Investigations and GAO explored tests directly marketed to consumers. In its investigation, GAO found that these tests provided

individuals with a wide array of results, with little consistency from test to test. And given the impact on patients of the results of these tests, whether leading some to miss real risk and others to seek treatment they don't need, it should be clear that the information LDTs provide is of grave consequence, and that is why many of the major cancer advocacy groups welcome greater FDA oversight. In response to the FDA's announcement, Calaneet Balas, Chief Executive of the Ovarian Cancer National Alliance, said, and I quote, "We in the ovarian cancer community know firsthand the danger of a test that hasn't gone through FDA approval. Oversure and early detection tests for ovarian cancer came to market in 2008, without independent verification and oversight, and this test didn't accurately predict ovarian cancer cases, leading otherwise healthy women to have their ovaries removed based on bad information. When a test routinely provides false positives, it is a problem, however, when that test is used to diagnose and treat cancer, it is a potentially fatal problem for millions of patients, and the clear demonstration of the need for greater FDA oversight."

I believe, Mr. Chairman, we have a responsibility to provide patients with greater certainty. Furthermore, we want to empower the medical community to harness these new technologies to improve patient health and outcomes, and eventually perhaps bend the lost curve. And while doctors have years of training and their patients' interests at heart, they are only as good as the tools they use. Physicians need to be able to trust the results of diagnostic tests so they can develop effective interventions.

It seems to me that regulating LDTs and other tests differently based on who makes them doesn't make sense. This is especially true given the scientific progress that has enabled lab-developed tests to have even greater impacts, both for good and for bad. If we want to promote the development of personalized medicine, which I think we all recognize is the future of medicine and the foundation of 21st Century Cures, then we need to ensure that highly complicated and potentially groundbreaking advances are clinically valid.

So, Mr. Chairman, this regulatory proposal has been in the work for some time, so I think we are all eager to hear from FDA about it. In addition, I look forward to hearing from other stakeholders about their views of the FDA proposal, because it is critical that its implementation ensures the safety of patients, but also allows for the continued advancement of cutting-edge personalized medicine, and I do not believe the two are mutually exclusive, but rather can be mutually supportive.

I also wanted to tell you again I enjoyed coming out to Lancaster for the field hearing that we had a few weeks ago.

Thank you.

Mr. PITTS. Thank you. That was very productive and thank you for coming out.

Chair now recognizes the Vice Chairman of the Subcommittee, Dr. Burgess, 5 minutes for an opening statement.

**OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. BURGESS. Thank you, Mr. Chairman, and let me agree with Mr. Pallone that the Cures roundtable that you had in Lancaster was very worthwhile, and I think we all learned a lot. It is just ironic that as we are proceeding with the Cures Initiative, and trying to remove some of the barriers, we are trying to facilitate the faster Cures, the promise of the 21st Century, that this morning we are having a hearing on what I consider to be a potential new roadblock or bottleneck on that path to Cures.

I have been to every Cures event here in D.C., I have been to several around the country. Repeatedly, we hear the potential for genomic medicine to help us understand illness, quickly diagnose it, and target treatment. This has been embraced in a bipartisan manner, and I strongly believe in that potential. Here is an example. A few months ago, the Centers for Disease Control briefed my office on an emerging global threat in the form of a virus. They had sequenced the virus, provided information to researchers, and even knew where in the particular country's jungle the virus had originated. It was impressive, to say the least.

Here is another one. Back in 2009, H1N1, and many of us remember, that subtype of the influenza A virus spread very rapidly. During the first week of the outbreak, 16 laboratories had laboratory-developed tests that could identify H1N1 from other H1 viruses. Most were available within 24 hours. The speed helped inform public health reactions. The FDA had no approved commercial kit, however, if they had, under this proposed framework which we are discussing this morning, if they had had a test, even if it was much older and inferior, these laboratory-developed tests would have been blocked from doctors and public health officials.

The Food and Drug Administration regulation of tests like these will be burdensome, and will slow the ability of clinical laboratories to develop tests that can allow us to respond to public health crises when they occur. This is also duplicative. Congress established a regulatory framework applicable to labs and laboratory testing, known as the Clinical Laboratory Improvement Acts of 1988, or CLIA. I am concerned that additional review of certain tests may be warranted, but previously I did introduce legislation to meet patient needs and ensure tests are accurate, reliable, and clinically valid by making improvements to CLIA, not replacing it. I authored Section 1143 of the Food and Drug's Safety Innovation Act so we would be able to discuss how patients, the practice of medicine, innovation and the economy could be harmed if the FDA tried to fit laboratory-developed tests into a misaligned definition of a medical device.

I fundamentally believe that the FDA has no statutory authority to regulate laboratory-developed tests. For FDA to have jurisdiction, it must have a traditional device and be commercially distributed among the states. LDTs do not fall under either category. Professional medical services are currently not regulated by the FDA, and I do not believe they should be.

In addition to these significant jurisdictional issues, the process the Food and Drug Administration is considering is of great concern. Even the courts determined that the FDA authority over lab-

oratory-developed tests, the Agency would need to amend its current regulations through rulemaking. The Food, Drug, and Cosmetic Act, the Administrative Procedures Act of the Supreme Court all require disseminating rules to modify current regulation, or to create legally-enforceable regulations. Instead, the Agency continues on with its jurisdictional power grab by attacking innovation, threatening professional practice, and risking jobs in order to claim authority over everything they see. They are doing this even at the expense of allowing the core mission of the FDA to suffer as a consequence. I can't think of a worse result: denying patients and doctors innovative tests, while redirecting resources that could be used to approve the next miracle drug or device.

Mr. Chairman, I would ask unanimous consent to insert into the record a statement by the American Medical Association on the topic of this hearing this morning.

Mr. PITTS. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. BURGESS. And further, Mr. Chairman, I would also like to submit into the record a copy of a bill, Senate Bill 796, introduced March 23 of 2007, by Senator Obama and Senator Burr, and this was the personalized medicine for all Americans by expanding, accelerating genomics research and initiatives, and one of the key parts of this legislation was to create within CLIA a specialty area for molecular medicine and genetics and clinical tests, instead of supplanting CLIA with the FDA, this proposal would have actually modernized CLIA in an approach that I think would be much more useful. So I will submit a copy of this legislation for the record also.

I appreciate the indulgence, and I am going to yield back.

Mr. PITTS. Without objection, so ordered.¹

Mr. PITTS. All Members' opening statements will be made a part of the record.

We have two panels today. On our first panel, we have Dr. Jeff Shuren, Director, Center for Devices and Radiological Health, U.S. Food and Drug Administration. Thank you very much, Dr. Shuren, for coming today. You will have 5 minutes to summarize, and your written testimony will be made a part of the record. So at this point, Dr. Shuren, you are recognized for 5 minutes for an opening statement.

STATEMENT OF JEFFREY SHUREN, M.D., J.D., DIRECTOR, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, FOOD AND DRUG ADMINISTRATION

Dr. SHUREN. Mr. Chairman and Members of the subcommittee, thank you for the opportunity to testify today.

FDA's risk-based proposal for oversight of laboratory-developed tests, or LDTs, is intended to ensure that patients and their health care providers make major medical decisions based upon accurate, reliable, and clinically-meaningful test results, while encouraging development and access to new tests. It would focus on those LDTs that pose the greatest risk to patients if the results are not accurate.

¹The information has been retained in committee files and is also available at <http://docs.house.gov/meetings/IF/IF14/20140909/102625/HHRG-113-IF14-20140909-SD009.pdf>.

FDA historically exercised enforcement discretion over LDTs, namely, we opted not to enforce requirements LDT makers were subject to, because back in 1976, LDTs were limited in number, relatively simple tests, and typically were used to diagnose rare diseases and uncommon conditions. LDTs offered today, however, are often very different from those 40 years ago. These tests have increased in both complexity and availability, and many are now used to diagnose common diseases and conditions. Increasingly, patients and their health care providers are relying on the results of LDTs to make major medical decisions. This evolution in complexity and volume has significantly increased patient risk of harm from higher-risked LDTs, and in some cases, there were already FDA-proved tests available; tests proven to be safe and effective. So using an LDT may put patients at unnecessary and avoidable risks.

These risks are not theoretical. There are cases of faulty LDTs for cancer, infectious diseases, heart disease, and other conditions leading to the wrong diagnosis, sometimes resulting in the wrong treatment, or the failure to treat when an effective therapy is available, and resulting in unnecessary costs to our health care system and American taxpayers.

Numerous stakeholders believe the current system of uneven oversight is having a negative impact on innovation. Conventional device manufacturers may go through the premarket review process and obtain clearance or approval for an IVD kit, only to be faced with immediate competition from labs manufacturing and marketing similar tests which did not obtain premarket review or meet other requirements to assure their tests are accurate and reliable. This has created disincentives for them to invest in developing innovative tests, and creating more U.S. jobs. But we have also heard from some academic medical labs that they make tests to address unmet needs, because there are no FDA-approved tests. We understand the value of and the need for these types of tests. Therefore, after listening to the perspectives from a broad range of stakeholders, we opted not to propose the same level of oversight for all the LDTs, nor to create a completely level playing field between tests developed by labs and those made by conventional manufacturers. Instead, we would continue to exercise enforcement discretion for many LDTs, including those that are low risk, LDTs for rare diseases, LDTs for unmet needs where no FDA clear or approved test exists for that specific intended use if made by a health care facility responsible for the care of the patient. FDA would also focus on high and moderate risk LDTs, and phase-in premarket review requirements for this subset over 9 years using a public process that includes expert advisory panels, as even recommended by the lab community. This flexible approach would balance the importance of accurate test results, with the need to facilitate innovation and prevent disruption of access to diagnostics. The more narrowly tailored and balanced oversight approach that we would propose for LDTs is also critical to the success of personalized medicine. Getting the right treatment to the right patients depends upon having accurate and reliable tests to identify who are, in fact, the right patients, and who should not receive a treatment that can cause them harm but provide no benefit. LDTs that steer patients

to the wrong treatments unnecessarily hurt patients, while jeopardizing the advancement of personalized medicine altogether.

We seek to facilitate innovation and test development, and we seek to assure that tests are safe and effective. The issue should not be do we regulate, but rather how we should regulate to best achieve both of these important objectives, the dual objectives that are at the core of the FDA's statutory mission: to protect and promote public health. Patients deserve no less, and our health care system can afford no less. That is the dialogue we need to have with laboratories, conventional device industry, as well as patients, providers, and other members of our medical device community.

So thank you for the opportunity to testify today, and I will take any questions that you may have.

[The prepared statement of Dr. Shuren follows:]



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT
OF
JEFFREY SHUREN, M.D., J.D.
DIRECTOR
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE
SUBCOMMITTEE ON HEALTH
COMMITTEE ON ENERGY AND COMMERCE
U.S. HOUSE OF REPRESENTATIVES

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

September 9, 2014

Release Only On Delivery

INTRODUCTION

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee, I am Jeffrey Shuren, Director, Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss the anticipated details of FDA's draft guidances, "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" and "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)," provided in a notification to Congress on July 31, 2014. The upcoming proposal for oversight of LDTs has been long awaited by industry, health care professionals and patients, and would be intended to close well known regulatory gaps and provide clarity regarding FDA's proposed approach for phasing in enforcement of regulatory requirements, including premarket review and adverse event reporting, for those LDTs that pose greater risk to patients if their results are not accurate. FDA oversight is critical to ensuring that patients and their physicians make major medical decisions based upon accurate test results. Providing clarity is also essential for attracting investment and accelerating innovation by clearly outlining FDA's expectations for those LDTs that we propose to phase in for review.

We listened closely to laboratories and many others viewpoints on LDT oversight in developing a balanced approach that supports continued innovation and patient access, while providing the appropriate protections that are essential as modern LDTs have become more complex and widely available in patient care. The Agency intends to continue exercising enforcement discretion for many LDTs – including those low risk LDTs that pose minimal risk to consumers, as well as those LDTs for rare diseases and unmet medical needs (those for which there is no FDA-approved or cleared test on the market). FDA's risk-based approach will promote innovation by ensuring that laboratories and conventional manufacturers alike have incentives to

develop new and better tests, while protecting patients. Finally, FDA oversight of LDTs is critical for the success of personalized medicine because getting the right treatment to the right patient depends on accurate and reliable diagnostic tests.

EVOLUTION OF LABORATORY DEVELOPED TESTS (LDTs)

LDTs are tests that are intended for clinical use and designed, manufactured and used within a single clinical laboratory. FDA has had the authority to regulate LDTs as devices since Congress amended the device definition to include all *in vitro* diagnostics (IVDs) in the Medical Device Amendments of 1976. The Agency historically exercised enforcement discretion over LDTs (i.e., generally did not enforce applicable requirements), as they were limited in number, were relatively simple tests, and typically were used to diagnose rare diseases and uncommon conditions. LDTs offered today, however, are often very different from those of the 1970s. These tests have increased in both complexity and availability, and many LDTs are now often used to diagnose common diseases/conditions, including those that are serious and life-threatening, and to guide therapy. Patients and their health care providers are making major medical decisions based upon LDT results every day, yet there is no assurance that they perform appropriately. This evolution in complexity and volume increases patient risk of harm from higher risk LDTs.

Without appropriate safeguards, neither patients, nor their health care providers, can be assured that many of these tests, particularly higher risk tests, are safe and effective. This is particularly troubling when an FDA-approved test is available, because it puts patients at unnecessary and avoidable risk.

We believe that LDTs serve an important role in health care and that there are many good tests on the market. Unfortunately, FDA is also aware of faulty or unproven LDTs, including problems with several high-risk LDTs such as: claims for diagnosing ovarian cancer that are not adequately supported with evidence; lack of appropriate controls yielding erroneous results; and falsification of data for determining which breast cancer therapy would be most beneficial. FDA is concerned that people could initiate unnecessary treatment or delay or forego treatment altogether for a health condition, which could result in illness or death. Specifically, FDA is concerned that faulty or unproven LDTs could lead to: patients foregoing proven screening for cancer, increasing the risk that their cancer will not be caught until it has reached an advanced stage; patients being over- or undertreated for heart disease; cancer patients being exposed to inappropriate therapies or not receiving effective therapies; incorrect diagnosis of autism; patients being prescribed unnecessary antibiotic treatments; and patients being exposed to unnecessary, harmful treatments.

The need for additional FDA oversight of LDTs has been discussed since the mid-90s. The Department of Energy, the National Institutes of Health, two different advisory committees to the Health and Human Services Secretary, and the Institute of Medicine, have recommended additional oversight of LDTs and identified FDA as the agency to provide such oversight¹. This

¹ National Human Genome Research Institute (1997). *Promoting Safe and Effective Genetic Testing in the United States*. See <http://www.genome.gov/10001733>.

Secretary's Advisory Committee on Genetic Testing (2000). *Enhancing the Oversight of Genetic Tests: Recommendations of SACGT*. See http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf. Accessed September 16, 2010.

Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). U.S. system of oversight of genetic testing: a response to the charge of the Secretary of Health and Human Services. Washington (DC): Department of Health & Human Services; 2008 Apr. 276 p. Also available at: <http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS>

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is because FDA already has the expertise and structure to oversee IVDs, and LDTs are a subset of IVDs. In fact, FDA's Office of In Vitro Diagnostics and Radiological Health reviews hundreds of IVDs per year, including LDTs for which laboratories seek FDA clearance or approval. We have been reviewing IVDs since 1976 and would review LDTs through our existing review structure. For the past several years, to support all of our IVD work, FDA has also been proactive in recruiting scientists with expertise in genetics, molecular technologies, and complex statistics so that novel diagnostic products could be reviewed in a timely and scientifically sound manner. Finally, adverse events are not systematically reported or collected for LDTs; the Agency has a mechanism for reporting and tracking adverse events that would enable doctors, patients, and the public to report on and learn about significant adverse events caused by individual LDTs, and, as with other IVDs, it would help FDA identify problems and take appropriate action, such as removal of unsafe products from the market. This is another critical feature of FDA's existing oversight structure for medical devices, generally.

RISK-BASED, PHASED IN APPROACH FOR TAILORED OVERSIGHT

FDA believes that oversight for those LDTs that pose greater risk to patients is critical to prevent physicians from failing to provide beneficial treatments, ordering unnecessary tests, providing unnecessary or harmful medical treatments. At the same time, FDA does not want to delay access to potentially important tests if there is no approved test on the market and does not believe that FDA oversight is necessary for low-risk tests. For these reasons, rather than draft a framework that proposes the same level of oversight for all LDTs, we intend to propose a risk-based oversight framework. Under this framework, FDA intends to continue to exercise enforcement discretion with respect to premarket review and good manufacturing practices requirements for certain LDTs. These LDTs include:

- Low-risk LDTs,
- LDTs for rare diseases,
- Traditional LDTs, namely tests of the type for which we originally intended in 1976 to exercise enforcement discretion and
- “LDTs for Unmet Needs”, tests where no FDA cleared/approved in vitro diagnostic exists for that specific intended use. FDA recognizes that labs may be the first to create certain innovative tests that fill unmet needs when the needs arise directly in the context of patient treatment. FDA intends to exercise enforcement discretion with respect to premarket review and good manufacturing practices requirement for LDTs for unmet needs unless and until such a test is cleared or approved by the FDA, because at that time we would have a high- or moderate-risk test we know is safe and effective. Continuing to use an unapproved test would then expose patients to avoidable risks given that an approved test exists.

LDTs for law enforcement purposes and certain LDTs for transplantation would generally remain under enforcement discretion with respect to all FDA requirements. This balanced approach would enable the Agency to focus on ensuring the accuracy of tests that are of high- and moderate-risk and that would have the most potential for harm to patients if the tests were faulty or inaccurate.

FDA enforcement of premarket review and good manufacturing practices requirements for high- and moderate-risk LDTs would be phased in overtime, beginning with the highest-risk tests. Twelve months after finalization of the proposed framework, laboratories developing the following high-risk LDTs would be expected to submit a premarket application for such LDTs:

- LDTs with the same intended use as FDA-approved or cleared companion diagnostics,

- LDTs that have the same intended use as an FDA-approved Class III device, and
- Certain LDTs used to determine the safety or efficacy of blood or blood products.

We would phase in oversight of any remaining high-risk LDTs over the following four years, and then would phase in oversight of premarket review and good manufacturing practices requirements for moderate-risk LDTs over the subsequent four years. This phased in approach would provide transparency for all stakeholders – it would clearly set forth FDA’s expectations, while allowing appropriate time for compliance with premarket review requirements for those LDTs that are affected.

Another feature of FDA’s upcoming proposal, which would balance the importance of ensuring accurate test results for patients with the need to prevent disruption of access to diagnostics, is our intent to provide laboratories with the option of notification, in lieu of registration and listing, for their LDTs. Within six months of finalization of the risk-based oversight framework, labs could choose to notify FDA that they are developing LDTs. This will enable FDA to better understand the current number and range of tests being offered, and to classify and prioritize these tests according to risk. Laboratories, pathologists, and industry have advised us of their interest in being engaged in this process and, therefore, FDA intends to use an open and transparent process for this prioritization. FDA intends to provide this notification information to advisory panels that will assist the Agency in classifying tests according to their risk and to assist in the prioritization of enforcement of premarket review requirements. Utilizing advisory panels for risk classification is consistent with the original process for classification of devices under the Medical Device Amendments, and recommendations from laboratories, pathologists, and industry, and allows expert opinion to be considered when both classifying based on risk as well as prioritizing enforcement of regulatory requirements on LDTs. FDA intends to propose

that those labs that choose to notify the FDA would generally remain under enforcement discretion with respect to the registration and listing requirements. This makes notification a less burdensome alternative, and it would not trigger the registration fee. The option allows FDA to collect and analyze the notification data that advisory panels will need in order to advise the Agency on appropriately classifying and prioritizing LDTs based on risk. This will also support FDA's goal to provide clarity to industry as the Agency plans, within 24 months of finalization of the risk-based oversight framework, to publish additional guidance that would clarify the types of devices that are Class I, II, and III LDTs to help manufacturers determine, among other things, whether they are likely to have an LDT that is low-risk.

As appropriate, FDA intends to leverage the expertise of individuals who already work with clinical labs. Specifically, FDA plans to explore opportunities to certify third parties to conduct premarket review of moderate-risk tests under FDA's existing third party program. We also would work with the lab community to leverage clinical studies published in the literature to support the review of their tests, if appropriate.

There are a potentially large number of tests now being marketed as LDTs that do not meet the definition of an LDT being proposed in the upcoming draft guidance document. To ensure continuity in the testing market and to avoid disruption of access to these tests, we intend to apply the same risk-based oversight approach to these tests, even though we would not consider them to be LDTs.

FDA OVERSIGHT IS IMPORTANT FOR INNOVATION

We appreciate concerns from laboratories and others about the FDA oversight proposal, and intend to propose a framework that prioritizes attention on those tests that have the potential to pose the greatest risk to patients and the public health if they do not work as intended. It is important to note that we have received input from numerous stakeholders who believe the current system of uneven oversight has had a negative impact on innovation. When conventional IVD manufacturers comply with FDA regulations and labs developing similar tests do not, this creates a lack of consistency across the diagnostic market. Conventional diagnostic manufacturers who have invested in the development of an IVD generally obtain premarket approval or clearance before packaging their tests into kits for use in multiple labs or health care facilities. They also register with the FDA, list their devices, report adverse events and comply with good manufacturing practices. They are concerned that their laboratory competitors are currently not doing any of this, yet offer immediate competition to their own FDA-authorized tests.

We believe the approach that we intend to propose for those LDTs for unmet medical needs would continue to allow development of innovative and necessary tests. As mentioned, the Agency intends to continue to exercise enforcement discretion with respect to those LDTs for which there is not an FDA-approved or cleared IVD on the market.

PERSONALIZED MEDICINE

The oversight framework we intend to propose for LDTs is important to the success of personalized medicine in the United States. Innovative tests developed by conventional IVD

manufacturers already are reviewed by FDA to assure they are safe and effective. They include genetic tests that help oncologists decide whether a patient is a good candidate for a drug that treats melanoma as well as tests that are capable of sequencing the entire human genome. Identification of the underlying genetic cause of one's disease, and treatment with a therapy that specifically targets that disease, has translated into greater efficacy and minimized safety risks for patients who might not respond to a particular treatment. This has been particularly evident in cancer, where new drugs are often developed with companion diagnostic tests.

LDTs are a subset of IVDs. Thus, LDTs that steer patients to the wrong treatments are a concern for patient safety and could jeopardize the advancement of personalized medicine. Inaccurate LDTs which indicate that patients are at high risk for a life-threatening cancer when they are not – or that they are at low risk for diabetes when they actually are at high risk for this chronic disease – does not benefit patients or health care providers and can cause harm. It is likewise not helpful, and may be harmful, when tests tell them they need higher or lower doses of widely-used drugs, when the opposite is true. Personalized medicine is built on two fundamentals: the reliability and accuracy of tests used to diagnose the underlying cause of a patient's disease or condition, and the safety and efficacy of therapies used to treat it. In order for us to continue the success and progress we have seen, it is imperative that test results are accurate. The current system of oversight for LDTs is not adequate to support the advancement of personalized medicine.

CONCLUSION

FDA recognizes the importance of implementing a balanced approach that fosters the development of new and innovative tests while ensuring appropriate patient protections. Like conventional IVDs, some LDTs may present significant health risks to patients if the results that

they generate are not accurate, while others present a much lower risk. We believe the tailored framework we intend to propose would strike the right balance by providing a risk-based, focused approach to the oversight of those LDTs that pose greater risk to patients, and that would phase in review for this subset of LDTs over time. FDA intends to continue to exercise enforcement discretion for many LDTs – including those that are low risk, for rare diseases, and for unmet medical needs. Our upcoming proposal would incentivize innovation, and would also support the advancement of personalized medicine by assuring that patients and their physicians can rely on LDT results for making major medical decisions.

Thank you for the opportunity to testify today about the anticipated details of FDA's risk-based regulatory oversight framework for LDTs, and actions that FDA is taking to support innovation and personalized medicine. I am happy to answer questions you may have.

Mr. PITTS. The chair thanks the gentleman.

And we will now go to questioning. I will begin the questioning, and recognize myself 5 minutes for that purpose.

Dr. Shuren, issuing this guidance document would constitute a significant change to almost four decades of Agency policy. It goes well beyond a set of recommendations or a description of current Agency thinking. How would implementing this new regulatory framework via guidance comply with the Administrative Procedures Act?

Dr. SHUREN. So we have in place what we call an enforcement discretion policy. Labs are currently subject to the requirements of the Food, Drug, and Cosmetic Act. We have, as a matter of policy, opted not to enforce compliance. Those kinds of general policy statements where we are not imposing a new requirement, that requirement is there but we are enforcing it, we are not interpreting legal norms, are not subject to Administrative Procedures Act to rulemaking.

Mr. PITTS. Understanding this approach would be a departure from existing practice, and have a substantial impact on regulated industry. Is the FDA not required to proceed with notice and comment rulemaking?

Dr. SHUREN. No. Under the Administrative Procedures Act, this change in enforcement discretion policy is not subject to those requirements.

Mr. PITTS. If a company or any other individual or entity invest in the research and development of an innovative diagnostic test and it is approved or cleared by FDA, I feel as though labs should not be able to simply copy the technology and market their own version the next day. This is particularly relevant if the test was reviewed as a companion diagnostic in concert with a drug. How frequently does this situation occur, and what can we do to address it?

Dr. SHUREN. Well, our understanding is it does happen commonly. It has particularly occurred with some of our companion diagnostics. So one example is Roche made a drug for treating metastatic melanoma, and it only worked in a subset of patients so they had a diagnostic test to identify which patients should get the drug and which shouldn't. The day they go on the market, there are 9 other labs who say we make the same test; in fact, some of them said they make a better test. But the only clinical study, all that data, Roche had it. They are the ones who had the drug, they did the study. So those labs made these claims, they are saying that, in fact, they have a better test, but there was no data there to actually show it. Those are kind of the risks, and even Roche has said this has created disincentives for them to create new drugs for personalized medicine and have companion diagnostics.

Mr. PITTS. While I do have some concerns about the process by which FDA is proposing this new regulatory approach, patient groups have questioned whether there are gaps in the current system that are jeopardizing patients' safety. If that is the case, we must work together to address them, and in your testimony, you cite several examples where FDA is aware of faulty or unproven LDTs. Can you provide the committee with detailed descriptions of

each of the instances of harm you referenced, and any other adverse event or anecdotal data FDA has compiled that forms the basis for proposing this new regulatory framework?

Dr. SHUREN. Yes, we can provide you with more details. I will say too, one of the challenges here is that there is no requirement for reporting adverse events or related malfunctions, so you don't have a surveillance system in place to even identify problems. Many of these have been found because researchers looked at the data, the reports in scientific articles, whistleblowers have come forward, or sometimes the labs have come to us. We have seen the data, and, in fact, we were able to see, you know what, the data isn't good, this test doesn't work. And that is just the tip of the iceberg, because we don't have a system in place to actually identify problems.

One of the things we are proposing is having that system in place so we know when problems arise. This isn't bureaucratic, it is actually good medicine, so that if problems are there, we want to make sure they get fixed, and we are aware of it.

Mr. PITTS. You state on the one hand that all high-risk tests should be reviewed by the FDA, regardless of whether they are developed in a lab or manufactured as a kit. That may very well be necessary. You go on, however, to discuss that the Agency will continue to exercise enforcement discretion with respect to tests that do not have an FDA-approved equivalent. Are these consistent positions?

Dr. SHUREN. So we are trying to strike a balance between assuring that there is availability of tests in cases where there aren't tests, but to have some protections in place, some mitigations for the risks that occur in those settings where you may not have a properly validated test that we have been able to see to assure it is safe and effective. On the same token, if you do now have an FDA-approved test on the market and you have another test for the same intended use, then we should be reviewing it or go ahead and use the test that has been proven to be safe and effective. That is the balance that we tried to strike, and our focus still is on those higher-risk devices, because the low-risk devices we have said we are exercising enforcement discretion towards, regardless. All we ask is, tell us what they are, and if there is a problem, report it, but other requirements you do not need to comply with.

Mr. PITTS. My time has expired. I have a few follow-up questions on—with that question, but I will submit them to you in writing.

The Chair recognizes the Ranking Member, Mr. Pallone, 5 minutes for questions.

Mr. PALLONE. Thank you, Chairman Pitts.

Dr. Shuren, I want to start out with some basic questions about FDA's role with respect to LDTs. I know you described this in your testimony but I would just like to hear more.

Some have questioned whether FDA has the authority to regulate LDTs in the first place. Specifically, they say that LDTs are not medical devices at all, instead, they assert LDTs are services that are offered in one place, making them more akin to a form of practice of medicine than to an article that can be sold in state commerce.

So, first, can you respond to this claim? Why does FDA believe the Agency has the authority to regulate LDTs?

Dr. SHUREN. Well, LDTs are in vitro diagnostics. They are reagents, instruments or systems that are intended to be used to diagnose a disease or other condition. And essentially, at its core you have a process, you have instructions for use for how you prepare a specimen from the body, like blood, and then how you go ahead and examine and analyze it to identify a particular substance in there that then is linked to the diagnosis of a disease. And when you make that test, those various components, the reagents, the instruments, the device developer may not make those. They may assemble them together, put them out, or they may tell you what their instructions for use, their process, which components to use. Labs do the same thing; they develop this process which, by the way, is IP, they get patents on a lot of these, and then they put together those reagents or those instruments and assemble that device. And that is, in fact, a device, and they have that in commercial distribution. They are out there marketing those tests.

The law doesn't distinguish between who makes the test, it is just if you make the test, if you make the device.

Mr. PALLONE. All right.

Dr. SHUREN. And as for regulating, even CMS has recognized that LDTs are IVDs, they are subject to FDA oversight. Even labs have come in for approval. I have to tell you one lab, very vocal opponent, and they have orally and in writing publicly stated they don't make IVDs, they make services, but I have here their submission to the FDA in-house right now where they say here is our test, it is an in vitro diagnostic test. They describe the method, the process they made, and then they identify the various components that they don't make but they form part of the test.

Mr. PALLONE. OK. Well, let me follow up a little bit about, you know, how traditional device manufacturers differ from clinical labs with respect to LDTs.

The ACLA claims they are two totally different entities because manufacturers make and sell kits, while labs design, validate, perform, and interpret tests and furnish the results to physicians. And one question ACLA raises in its testimony is how to define where the manufacture ends and the performance begins.

So, again, I would like to know your response to that. Specifically, what is the implication, significance and relevance of that question for FDA regulatory purposes?

Dr. SHUREN. Yes, so we define who is a manufacturer that sits in our regulations, and essentially it is a person who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, or biological or other procedure. They make the test, they design the test, they develop the test. That is the manufacturer. When they perform the test, they are acting as more of a traditional lab. And a lab can do both, and some only do the testing, some develop the test and they perform the test.

Mr. PALLONE. All right, and then lastly, there has been a lot of concern about whether a stronger FDA regulatory stance with respect to LDTs might hinder the innovation that has been flourishing in this area. And that is obviously something we have to be concerned about.

Presumably, all sides would agree that there should be enough oversight of tests to ensure that they are accurate and clinically relevant, but the oversight should not be so burdensome as to prevent or unnecessarily delay the development of important new tests or the improvement of existing tests. The difficulty, of course, is in achieving that balance. Our second panel will have witnesses who believe your guidance appears to achieve that balance, and other witnesses who believe FDA is inherently the wrong agency to even attempt to achieve that balance.

So I would like to get your response to some of the criticism that is being leveled at your whole approach. How do you respond to claims that FDA's involvement will hinder innovation?

Dr. SHUREN. Well, our intent is try to strike the right balance. We have proposed a risk-based framework in which we continue to exercise enforcement discretion for a subset of LDTs to try to make them available, but by the same token, try to assure in other cases that we do have that proper validation that those tests are safe and effective. And the point for putting all of this out is, let us have that dialogue. If what we are proposing doesn't hit the mark right, then let us talk about what is the best way to hit that mark. Whatever we come up with, we are not going to satisfy everyone, I will tell you that. Whatever we get at the end of the day, someone is not going to be happy because there are so many different perspectives, but we are going to try to hit it the best as we can. And the real solution is we need the parties at the table, we need the lab community to come in and talk to us, to hopefully move away from, you don't have oversight for us, we don't want to talk, rather say, OK, we get it, let us figure out how to make this work. Let us hit that right balance on innovation and safety and effectiveness, the right balance on protect public health and promote public health.

Mr. PALLONE. All right. I thank you for your response. And I just think it is clear, we need to have the FDA overseeing these tests.

Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman.

I now recognize the Vice Chairman of the Subcommittee, Dr. Burgess, 5 minutes for questions.

Mr. BURGESS. Thanks, Mr. Chairman. Dr. Shuren, good to see you again. I am happy to hear you talk about a spirit of openness and cooperation. I just find it curious that my discussion with my own office staff and committee staff, there was no outreach by the FDA to talk about this prior to issuing the letter that you did at the end of July, triggering the guidance that you are putting forward. So I hope that perhaps you have just signaled a change in tone. I hope there is the willingness to indeed work with many of us who are concerned about this, and clearly the concern exists, you knew that because of the language that was in the FDA reauthorization bill, and again, I just find it curious you would not have had any discussion with committee staff prior to issuing that notice about guidance.

Let me just underscore something that the chairman asked you. Will you provide our committee with all internal FDA assessments of the harm that has been completed or were the bases for the Agency's concern in this proposed framework?

Dr. SHUREN. Well, we were asked if we could provide details on those cases, and we will provide the details as requested.

Mr. BURGESS. But all internal documents that you have received at the FDA that formed the basis of this decision, may we look forward to you sharing those with us in this new spirit of openness that you just proclaimed?

Dr. SHUREN. So let me go back and talk with people. When you say all documents, if I have draft documents, we usually try to move forward to things that are final and the completed information. So we want to get you everything that is right, and we will go ahead and do that.

Mr. BURGESS. Well, specifically, we are looking at how many of these tests are performed daily, what is the extent of the harm, have there been similar problems with FDA approved and cleared kits, and then lastly and perhaps most importantly, do you believe physicians are not concerned about patient harm?

Dr. SHUREN. Right.

Mr. BURGESS. So those would be the specifics that we would be asking for.

Now, we have had these discussions before, and I firmly believe the FDA lacks statutory authority to regulate medical practice. Laboratory-developed tests are a service and not commercialized devices.

Do you have or did you rely on any legal opinion or memo from FDA counsel, and if so, can you produce that legal guidance for us?

Dr. SHUREN. We did get guidance from legal counsel, and I will go back to them to see what materials we have or are able to provide.

Mr. BURGESS. It is critical that, again, that information be shared with us.

So let me ask you a question. In 30 days, we had asked for a notification 60 days prior to undergoing the guidance. So you notified us at the end of July, so what is going to happen in about 30 days, will the FDA be releasing guidance, draft guidance, or regulation based on this framework?

Dr. SHUREN. Our intent is to release draft guidance, to have a public process to get input on that, to have a dialogue that includes not only an open public docket, public meetings, opportunities to discuss in-person with us. We want to have an open dialogue moving forward, and that is the process. Very—

Mr. BURGESS. You—

Dr. SHUREN [continuing]. Public, very collaborative.

Mr. BURGESS. So the FDA is proposing to modify a regulation through a guidance document. Regulation the FDA specifically indicated it would not regulate laboratory-developed tests, so where is the legal authority for this decision?

Dr. SHUREN. Actually, we have been consistent for years that we do regulate LDTs. If you have statements that say that we don't have authority over LDTs, that would be helpful to see. We have always said we have authority. We haven't enforced requirements. That is a matter, that is decision on the part of the Agency, that is enforcement discretion, and that is what we have done. We are not changing a particular regulation, we are not imposing a re-

quirement that isn't already imposed upon the labs, but simply we have not been enforcing.

Mr. BURGESS. Well, forgive me, but enforcement discretion does not give me a warm fuzzy feeling, and it is not just with this Administration, it was with the previous Administration as well. We are all familiar with the statement, "I am from the government, I am here to help." We are not going to bother you because we have enforcement discretion, so we won't bother you up until the day that we do. Most people find that as a very nebulous framework in which to work, and a very difficult framework in which to plan, plan for the future and plan for expenses.

So how will this all work? Guidance should not, and the courts have determined does not, have the enforcement power of regulation, so how does the FDA intend to bring this framework upon the world and have it function without clear authority from Congress, and without providing the normal regulatory framework?

Mr. SHUREN. Well, again, there is authority under the statute and that authority is there and it is applied now. We haven't enforced it. And while this discussion isn't new, we have been talking about enforcing those requirements in LDT as the existing requirement since the 1990s. We have been called upon by the Department of Energy. We had two Secretary Advisory Committees, Secretary of HHS, saying that we should be exercising our authority over LDTs. The Institute of Medicine came back to say that. In 2007, we issued draft guidance withdrawing enforcement discretion for a subset of LDTs, but the lab community came back and said please don't do this piecemeal because that is not predictability for us. Please instead put in place an overarching framework. Seven years later, 7 years later, that is what we are doing, 4 years after we had a public meeting in 2010 to do this. This is no sudden change; this is years. The question shouldn't be where did this come from, the question should be, FDA, what the heck took you so long?

Mr. BURGESS. Mr. Chairman, I have additional questions which I will submit for responses in writing, and look forward to the speedy responses, and yield back.

Mr. PITTS. The Chair thanks the gentleman.

I now recognize the gentleman from Georgia, Mr. Barrow, for questions. No questions? Who is next? The chair recognizes the gentleman from Virginia, Mr. Griffith, 5 minutes for questions.

Mr. GRIFFITH. Thank you very much, Mr. Chairman.

I am going to follow up a little bit, although maybe a little different than what Dr. Burgess was going after. And I understand some of the concerns, but the Supreme Court has held that an agency has a right to change its policy so long as it supplies a reasoned analysis for that change. An agency, however, may not change its policies in a way that simply disregards rules that are still on the books. FDA's current regulations specifically exempt clinical labs from medical device registration and listing requirements.²¹ C.F.R. 807.65(i).

In an attempt to avoid directly conflicting with this regulatory exemption, the proposed guidance documents claim not to require a clinical laboratory to register and list their tests, but to create a new notification option where labs could notify the FDA of the

types of LDTs they develop. If, however, a lab does not submit a notification, it will then be subject to registration and listing requirements, along with the related fees.

Now, it doesn't seem like there is a whole lot of choice in there. So, Dr. Shuren, where in the statute does FDA claim the authority to establish such a notification process?

Dr. SHUREN. So the labs are currently subject to registration and listing. Our interests for many of these is to know which are the LDTs out there so we can use that information to then determine the risk classification for them. We have offered as an option for not complying to provide the notification. I will tell you the reason we did it. If you notify and you don't do, instead, registrational listing, you are not subject to the device tax. That is what we did, plain and simple.

Mr. GRIFFITH. Because there is a lot of pressure regarding the medical device tax?

Dr. SHUREN. No. We, in looking at this, said, you know what, for a lot of these too, if we are not going to then subsequently actively regulate them, because they are going to be under enforcement discretion, we weren't going to trigger all the other things that come with that. And that is what we tried to do, we were trying to give labs a break.

Mr. GRIFFITH. If a lab fails to submit a notification and is therefore subject to registration listing, how would this not directly conflict with the FDA's current regulations?

Dr. SHUREN. I am not aware that there is a conflict with current regulations.

Mr. GRIFFITH. You know, you indicated earlier, and I thought this was kind of interesting based on some of the things I have read, that it is not a question of, and I am paraphrasing a little bit, but it is not a question of do we, but how we regulate, and yet by doing guidance, you are not going through the normal administrative process active procedures, and there is a lot of concern that folks won't be able to get their input put into the Agency.

So if it is a question of do we—not do we, but how do we regulate, shouldn't you be going through the APA?

Dr. SHUREN. No. So, again, this is a general policy statement. These requirements already apply. They are supposed to be complying with it. We are not enforcing those requirements as a matter of policy. Making those changes, the Administrative Procedures Act does not impose rulemaking on those kinds of policies.

However, you raised the point about input, because notice and comment is about do I have the opportunity to provide input. In rulemaking, notice and comment is, yes, you can submit comments on the rule. In our guidance document, you will be able to submit comments on the guidance document. We will be holding a public meeting. We will have opportunities in other venues to talk about this. There will be lots of opportunity for public discussion, for people to get their viewpoints on the record or off the record. That is what we will do so we can have a fully informed decision. And we want to hear from people, so we ultimately hit this right.

I do want to get back to you on that particular regulation. The regulation pertains to labs who are using an FDA-approved test, not to labs when they are making an FDA test. When they are

making the test, they then become a manufacturer. It triggers all the requirements. That is what the regulation is about.

Mr. GRIFFITH. I think there is some disagreement on that, and it clearly is not what is stated in the regulation. It just says clinical laboratories are exempt under Part 807 as well, but anyway.

With that being said, Mr. Chairman, unless somebody else would like my time, I will—well, Dr. Burgess, I yield to Dr. Burgess.

Mr. BURGESS. Does the gentleman yield for the last few seconds?

Mr. GRIFFITH. You got it.

Mr. BURGESS. Let me just ask you a question, Dr. Shuren, as far as the scalability. I mean do you have the personnel, the resources? We are constantly confronted during the Cures Initiative discussions that the FDA is kind of behind in its information architecture. Do you have the personnel and the scalability to take on this vast new regime that you are proposing?

Dr. SHUREN. One of the reasons we proposed the long phase-in was in part so that labs could have the time to get used to the framework. The second is taking into account our resources so that we are not imposing these day one. The phase-in on premarket review is over 9 years, so that we are able to then identify based upon risk, calling in in segments these particular tests those who would be subject to review, and then there are a number that will still be under enforcement discretion, but those that would be—

Mr. BURGESS. Will you collect user fees from those labs?

Dr. SHUREN. For which ones?

Mr. BURGESS. For the labs that you are now regulating under guidance.

Dr. SHUREN. So for the ones who come in in premarket review, we actually have the authority to waive fees, and one of the reasons was put into MDUFA III when we did this with the device industry was specifically for that purpose, that if we withdrew enforcement discretion on labs during MDUFA III, we would have the ability not to enforce user fees, but then the labs should be at the table for those discussions. Now, we invited them to the table for MDUFA III, they declined to come, but we would hope if we are moving forward then they would come to the table in MDUFA IV and then let us talk about that, but for right now, we have the ability to waive fees. Again, none of this starts until we are out with final guidance. We still have to get the proposed guidance out, go through the public process, then final guidance, and then the first round for submissions doesn't start until a year after that for premarket review.

Mr. BURGESS. I yield back to the gentleman.

Mr. GRIFFITH. And, Mr. Chairman, I would also ask—Dr. Burgess previously asked the question about legal memorandums, and if we could have both in-house and outside counsel memorandums if they exist. And I yield back.

Mr. PITTS. The chair thanks the gentleman.

I now recognize the gentleman from Texas, Mr. Green, 5 minutes for questions.

Mr. GREEN. Thank you, Mr. Chairman. Again, welcome.

I understand the number of FDA cleared or approved tests represents a small fraction of the tests relative to the number of LDTs. Do we know how many LDTs are actually out there?

Dr. SHUREN. We don't have an absolute number on those, in part because there is no system on notification where you put them in a database. We have estimates of what we think are out there.

Mr. GREEN. OK. Given the number of LDTs that are now the subject of premarket review under this proposed framework, how will FDA implement this proposal and will additional resources be needed?

Dr. SHUREN. So, again, the phase-in was an attempt to try to fold this in with the current resources that we already have, and, again, during this time, tests remained under enforcement discretion. So if it turned out, as we get a better lay of the landscape of what is out there, if we need more time on implementation or for review, we can do that, it is not going to put that lab to have to take that test off the market. And if it turns out there is a need for additional resources, that is the kind of conversation we have as a part of user fee reauthorization.

Mr. GREEN. I have heard that——

Dr. SHUREN. And then there were discussions about legislation previously, and I do know when CMS looked at that bill, they thought that the cost for that would be about \$50 to \$100 million to implement, starting with \$20 million at the outset to create a duplicative bureaucracy. And that isn't the best way of investing dollars or spending dollars, to simply rogue government and have duplicative oversight, and a costly one. So here we have experts already, we are leveraging them to do their kind of work they do every single day and they have been doing for decades, and now let us fold this in with the resources we have and if we need to address more, we will have those conversations——

Mr. GREEN. OK.

Dr. SHUREN [continuing]. And user fee discussions.

Mr. GREEN. OK. I have heard the proposed framework would actually put the FDA in the business of regulating the practice of medicine, since LDTs is a service rather than medical device. How does FDA respond to this assertion and at what point is LDT a medical device, when does its use, interpretation, application, and modification become a service provided by a pathologist or physician on behalf of a patient? What is the breaking point?

Dr. SHUREN. Well, again, if they are making the test, all right, and that can be as a manufacturer assembling the test, they have developed the process and they put it together then with reagents and instruments, and now they are out there marketing it, they have made a test. When they are running the test, they are performing the test, then they are acting as a laboratory, then providing a service. That is subject to oversight under CLIA. The FDA framework is complementary to assure the safety and effectiveness of the tests that they use, whether that is made by someone else or they make it themselves in the laboratory.

Mr. GREEN. OK. Under the framework, will professionals working in CLIA-regulated labs be treated as both device manufacturers and users?

Dr. SHUREN. So if they are making tests, then we would treat them as a manufacturer, keeping in mind that for a variety of categories of LDTs, we are still exercising enforcement discretion. So even though they make a test, like a test for an unmet need, we

are saying to them tell us what it is, report problems, but otherwise you don't have to come in for premarket review, you don't have to put in place quality systems, the kinds of controls to assure that when you make a test, you make a high-quality test.

Mr. GREEN. But they are actually manufacturing it and using it, so does this framework create a duplicate system, regulatory oversight between CLIA and FDA?

Dr. SHUREN. No. We view these as complimentary. CMS views them as complimentary. In fact, even when CLIA was passed in 1988, the then-administrator of what was the Health Care Finance Administration, former name for CMS, Bill Roper even said CLIA is complimentary to what FDA does. But we really need both. If labs are in the business of acting as manufacturers and making tests, then there is complimentary of FDA oversight to assure the tests are safe and effective, and there is CLIA oversight to assure that the services that are performed by the laboratory are done at high quality, that the people are appropriately trained.

Mr. GREEN. Well, the history of our committee, we sometimes have trouble for two agencies actually trying to cooperate together, and sometimes it takes statute to do it, but looking at the future of medicine, the importance of innovation and effective diagnosis are impossible to overestimate, and looking forward to working with the FDA, the committee and the stakeholders to see that the regulatory framework ensures patient safety while unleashing the potential for LDTs and diagnostics in general. So, discretion is important and the partnership between the two agencies is really important because we don't want to stop the success that we are seeing in that individual health care.

Thank you, Mr. Chairman. I yield back.

Mr. PITTS. The chair thanks the gentleman.

I now recognize the gentleman from Illinois, Mr. Shimkus, 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman. It is great to be here. Dr. Shuren, welcome.

Just on a side, over the break, we had a 21st Century Cures panel hearing in the State Capitol of Springfield. It just went phenomenal. I think there is a lot of excitement on both sides and in the health care communities, and I hope we can keep moving forward, and I know this isn't really specifically about that, but there is a new era coming in health care delivery and the like, and I just wanted to report back that that was a very productive hearing we had, Mr. Chairman.

So, Dr. Shuren, again, welcome. Under the practice of laboratory medicine, CLIA requires disclosure of known information relevant to use of a test by a certified laboratory to a treating physician, without regard to, and I quote, "labeling claims." This proactive approach to dissemination of information by a clinical laboratory may be inconsistent with the restriction on dissemination of information by a medical device manufacturer under FDA regulation.

How would FDA manage conflicting requirements governing consultations with physicians about patient test results?

Dr. SHUREN. So we don't view that as in conflict because the labs can have those kind of communications. That does not run afoul of the Food, Drug, and Cosmetic Act.

The issue becomes if they are out there promoting, they are marketing I have this test that I can perform, and if they are marketing it in a case where they should have come in for review, they need to come in for review, but they can have those discussions with treating physician—treating physician can ask them to run a test in an off-label fashion. That is fine, that is not inconsistent with our program.

Mr. SHIMKUS. What types of diagnostic or patient treatment claims would be permissible, and what kinds of evidence would be required by the FDA?

Dr. SHUREN. Yes, so in terms of permissible, one would be permissible without coming to the FDA, and we have mentioned, well, first of all, the low-risk tests you don't come in anyway, and we have said we are exercising enforcement discretion for a number of the requirements. For rare diseases, we are continuing to exercise enforcement discretions. You don't come into us, where otherwise a conventional manufacturer would have to come into us. And even if there is an approved test for a rare disease, we are still saying you don't have to come into us.

If you are making a test where there is no FDA-approved or cleared test, you can go ahead and do that until the point where there is an FDA-approved test. Now, we have a mitigation in place which is a lab and a health care facility where you are treating that patient, or within that health care system, because you have a shared accountability for both testing the patient and treating the patient. That is the mitigation we have put in place because here, we don't have that independent validation the test is actually safe and effective, and that is a balance we have tried to put in. But then in other cases where, for example, we have an FDA-approved test, if you want to continue to market as such a test, you would come in the door, much like the other manufacturer, to show you are safe and effective, because at that point, we have a test we know which works. That is in the best interests of patients to use it. If you have one that is good, or you think you have one better, then provide the data to show you are better because you may not be, and if you are not, that hurts patients because doctors and patients can go, it is a better test, I will use that one, in fact, it may not be.

Mr. SHIMKUS. Great. On the medical device quality system regulation requirements would apply upon filing of a premarket submission with the Agency, but the draft guidance does not adequately tell clinical laboratories how to comply. As one example, what constitutes a malfunction of a finished device if the test is an LDT?

Dr. SHUREN. So a malfunction is where the test does not meet its performance specification, or it doesn't perform as intended. That is a malfunction, and that has applied for IVDs, and we have information about that.

Now, I will say in terms of the application of quality systems, we have been working with the Clinical and Laboratory Standards Institute on developing education modules about how quality systems would apply to laboratories, and to get that out there for better training for the labs so they have information, they have people who will have training programs with them, we will get feedback

on that. If people feel they need more information, we will work with the lab community on what they need to be successful, but we will have more information that is out there.

Mr. SHIMKUS. I thank you for your time.

And Chairman, I yield back.

Mr. PITTS. The chair thanks the gentleman.

I now recognize the gentlelady, Ms. Schakowsky, 5 minutes for questions.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. And I apologize, Dr. Shuren, that I just arrived from another meeting, but I did want to ask you an important question.

CMS, obviously, could not be here today to participate in this hearing, and I think it is unfortunate because much has been made of the role that CMS plays in overseeing LDTs under the authority provided by the Clinical Laboratory Improvement Amendment. To be sure, CMS plays a critical role in regulating laboratory practice in this country, but I think we need to be clear about the limitations of that role as well.

So I have a document that I obtained from the CMS Web site. It is entitled CLIA Overview, and it contains CMS's responses to several frequently asked questions, and I would like, Mr. Chairman, unanimous consent to enter this document into the record.

Mr. PITTS. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Ms. SCHAKOWSKY. So let me refer to a couple of excerpts that appear to explain the difference between the roles that CMS and FDA play with respect to LDTs.

First, this document states, "when a laboratory develops a test system such as an LDT in-house without receiving FDA clearance or approval, CLIA prohibits the release of any test results prior to the laboratory establishing certain performance characteristics relating to analytic validity for the use of that test system in the laboratory's own environment. This analytic validation is limited, however, to the specific conditions, staff equipment, and patient population of the particular laboratory. So the findings of these laboratory-specific analytic validation are not meaningful outside of the laboratory that did the analysis. Furthermore, the laboratory's analytic validation of LDTs is reviewed during its routine biannual survey after the laboratory has already started testing." And it goes on to describe the FDA's role. In contrast, the FDA's review of analytic validity is done prior to the marketing of the test system and, therefore, prior to the use of the test system on patient specimens in the clinical diagnosis/treatment context. Moreover, FDA's premarket clearance and approval process assess the analytic validity of the test system in greater depth and scope. The FDA's processes also assess clinical validity.

According to this document, CMS does not assess clinical validity. So let me ask you this. Here is the question. Can you please describe the difference between CMS's review of analytic validity and the FDA's review of clinical validity?

Dr. SHUREN. So for analytical validity, we dive into the data to make sure that, in fact, you have demonstrated there is analytical validity. And just so folks know, what you are doing there, it is the accuracy of measuring something in a human specimen. So let us

say measuring protein in the blood. So we do a deep dive into that to make sure, in fact, that validation was accurate.

In CLIA, it is a much lighter look. In some cases, it is a checklist to make sure you have it, or maybe a sampling of the analytical validity that has been done, not of all the tests.

Ms. SCHAKOWSKY. But—

Dr. SHUREN. And clinical validity is then the association of what you measure in the body with a disease, so that you, in fact, are making a diagnosis. This protein, if we find one of these markers, means you have this disease. CLIA doesn't have that. We have that to make sure then when you do the test, and people are doing a test to make a diagnosis, that, in fact, it is accurate in making that diagnosis. And the Web site for CMS also says as a result—and this is talking just about analytical validity, as a result, FDA review may uncover errors in test design or other problems with a test system. Errors that will not be found under the CLIA system. Again, they are complementary.

Ms. SCHAKOWSKY. So I just have a couple of—so how do you plan to coordinate then with CMS to make sure that we are getting the best data?

Dr. SHUREN. Yes, so we already work with CMS. We have a very close relationship. We are part of the CLIA program. When they talk about, to make an LDT you have to be in a high complexity lab, we make those determinations too regarding complexity. We make the determination on a waiver for complexity if they want to do some of these lower-risk tests. And in developing this framework, we have been in discussions with CMS. When we look at quality systems, we are in discussions with them too because there is a little bit of overlap—

Ms. SCHAKOWSKY. Yes.

Dr. SHUREN [continuing]. And our plan is not to duplicate those requirements, it is to just go with the pieces that are complementary. What we are doing with CLSI is also to focus on the parts that are different, not to sort of talk about the things that you may already be covering on CLIA, and then we don't need to touch that. In fact, we have proposed—we would propose to have the option for a third party review model for both moderate risk tests and for inspections, for audits. And we know some of the CLIA auditors are interested in being accredited by FDA to do those reviews, and to actually, when they are in the lab, to go look at it for CLIA to be able to do the additional look for FDA to try to minimize any disruption with the labs, and to work with those entities that they are already accustomed to working with.

Ms. SCHAKOWSKY. Thank you for that clarification. Appreciate it.

Mr. PITTS. The Chair thanks the gentlelady.

I now recognize the gentlelady from North Carolina, Mrs. Ellmers, 5 minutes for questions.

Mrs. ELLMERS. Thank you, Mr. Chairman, and thank you, Dr. Shuren, for being with us today.

I just want to go back and clarify some of the responses that you have given to some of the questions, because as this is going along, I am getting a little confused as to what the whole process is and why we are approaching this, or why the FDA has taken this approach.

One, I want to go back to the user fees and the medical device tax. Now, my understanding is, from what you have said, that the FDA has no intention of putting a tax on these lab tests, is that correct?

Dr. SHUREN. Well, and just to clarify, we don't handle the medical device tax. We have nothing to do with it.

Mrs. ELLMERS. But—

Dr. SHUREN. The trigger is registration and listing of that device then triggers—

Mrs. ELLMERS. OK, so—

Dr. SHUREN [continuing]. The device tax.

Mrs. ELLMERS [continuing]. The part that the FDA would play does not intend, can you definitively give us an answer today that this will not be an item that will be taxed for the American people?

Dr. SHUREN. So some of the tests and labs would be taxed if they are making a test that then has to come in for premarket review. If they opt for doing that, at that point then they would move over to register and list with us, because we have requirements—it is the registration and listing that then is the trigger for some of the other requirements.

Mrs. ELLMERS. So then this is open-ended? So this is—these tests can be taxed?

Dr. SHUREN. If they are the tests that have to come in for FDA—

Mrs. ELLMERS. And they are not presently being taxed?

Dr. SHUREN. They are not presently being taxed.

Mrs. ELLMERS. But they can in the future.

Dr. SHUREN. They can in the future.

Mrs. ELLMERS. OK, that is a good clarification right there.

Now, we talked a little bit about user fees as well between some of the labs that are being regulated. Can you just—and there again, I would just like to have you go back and discuss what you have already said, but I just need clarification.

Dr. SHUREN. Certainly. If our framework were to be implemented during the course of MDUFA III, we would not impose any user fees. We would waive those user fees. We have the authority to do that.

Mrs. ELLMERS. Now, you have the authority—

Dr. SHUREN. Right.

Mrs. ELLMERS [continuing]. But you can't say definitively today that that is not going to happen, correct? I mean—

Dr. SHUREN. That—

Mrs. ELLMERS [continuing]. That could be changed at any moment. The FDA could decide tomorrow that now we are going to institute user fees.

Dr. SHUREN. If the framework in place—yes, if people change their mind, but that is actually why we had expanded the waiver provision. It was intentionally put in. Now, for MDUFA IV, we would like to have the labs at the table to have that discussion, like we invited them for MDUFA III, come to the table in MDUFA IV and then talk about—

Mrs. ELLMERS. Yes.

Dr. SHUREN [continuing]. User fees. Should they apply, what should they look like, that is the discussion to have, just as we have with other device developers.

Mrs. ELLMERS. I want to go back again to where the origin of all this came from. My understanding is you have stated in your testimony and in discussion that FDA has always had this ability to put this forward, but has not in the past and now has determined to do so, is that correct?

Dr. SHUREN. Yes, we have the authority over LDTs, and subject to those requirements, we haven't enforced it.

Mrs. ELLMERS. Where did that come from, what statute, and when did it become part of the ability for the FDA to institute this? Can you go back, give us a date, a time, a rule?

Dr. SHUREN. So 1976, the law was changed to give us oversight on in vitro diagnostics. It is agnostic as to who makes it. That is the FDA law. It doesn't distinguish between who makes the test, it is if you make the in vitro diagnostic, that is where we have the authority. When CLIA was passed in 1988, which, remember, was an amendment to a 1967 law that put in all the licensing structure, that didn't change. Nothing that was changed in the law, there is nothing there on the legislative history, that authority for FDA simply persisted.

Mrs. ELLMERS. OK, now, what has changed now—

Dr. SHUREN. And even recognized by CMS when the law was passed.

Mrs. ELLMERS. And what has changed now that has caused the FDA to now look at this as something that needs to be implemented?

Dr. SHUREN. Yes, and keep in mind we have been looking at this for years. We have had these discussions starting in the 1990s, and even started taking steps in 2007 with the draft guidance to withdraw enforcement discretion for a subset of LDTs, and again, we heard from the lab community, don't do it piecemeal, do an overarching framework. Why we have done this is because the tests have changed. Years ago, these were very simple tests. They tended to be rare conditions, they were used locally. There were really within a facility and a treating physician, and you have the laboratory. Today, we have increasingly more complex and sophisticated tests, higher-risk tests, being used for common diseases, being used nationally, increasingly doctors and patients relying on the results of that test, and then examples of faulty LDTs. That has been the push, and the push doesn't just come from us, it is from outside bodies.

Mrs. ELLMERS. Can you cite for the committee or provide—I realize you probably can't do that right—at this very moment, can you give the committee those tests that have shown inaccuracies that you feel that the FDA needs to address this issue as tests have been innovated, and obviously you are seeing something that is indicating that we need to implement more regulation, and I would just like for you, if you could, to provide for the committee what those tests are that you feel are being—or are coming up with inaccurate results.

Dr. SHUREN. Yes, we will do that.

Mrs. ELLMERS. Thank you. Thank you.

And I apologize, Mr. Chairman, I went over on my time, but, yes, if you could provide the committee with that, that would be wonderful. Thank you.

Mr. PITTS. The chair thanks the gentlelady.

I now recognize the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions.

Mr. BILIRAKIS. Thank you, Mr. Chairman. I appreciate it very much.

During the August recess, I held two 21st Century Cures Roundtables in my district, and I heard from patients and some of their problems. I also heard from providers and some of their problems. There were two themes that came up: outdated payment policies and also the barriers to innovation. I am glad that we are holding this hearing today because the specific issue of FDA regulations of labs develop tests was one of these issues that came up. We had a company talk about their concerns that the FDA's regulations could slow innovation.

At the end of the day, we want safety, of course, but we also want to keep innovation products to get to the market. If we don't, then the patients, in my opinion, will suffer.

Dr. Shuren, I have a couple of questions. Has FDA done a thorough economic analysis that considers the direct cost to laboratories and taxpayers if FDA goes through with their guidance?

Dr. SHUREN. So we don't have a formal economic analysis. On the other hand, we also hear from labs who say, well, when we make tests, we validate them. CLIA says they are supposed to be validating those tests when they make them or they modify them. And so if that is the case and they have that data, the cost should be a lot less to be able to then provide that to us.

Mr. BILIRAKIS. Thank you. Under the Regulatory Flexibility Act, the RFA, federal agencies are required to assess the impact of their regulations on small businesses. The analysis should include such things as how many small businesses there are, the projected reporting, recordkeeping and other compliance requirements of the proposed rules, any significant alternatives to the rule that would accomplish the statutory objectives while minimizing the impact on small entities, and it requires agencies to ensure that small businesses have the opportunity to participate in the rulemaking process. However, if FDA goes forward with guidance and not formal rulemaking, it undermines laws that protect due process, such as the RFA or the Administrative Procedures Act.

Will the FDA go through with the traditional process of rule-making?

Dr. SHUREN. No, because this is a policy of enforcement discretion. The requirements are already there. They are subject to the requirements. We are not imposing that. We have, as a matter of policy, decided not to enforce them. We are now changing that policy and enforcing requirements in certain cases. Those general policy statements under the Administrative Procedures Act are not subject to rulemaking, and actually have significant impact if they are for our ability to do so. However, as part of the process with guidance, there is a public process for small businesses and others to weigh in, not only on the docket and written comments with public meeting, we will have meetings that are occurring in other

venues and other discussions. Some groups have already been in talking with us about the framework, and we will have that dialogue. What we hope is that people will come and talk to us, that the lab community will be in the door and have those conversations. Some have. We would like to see the full community come in the door, not talk about we provide services, these aren't IVDs, don't regulate us, but rather come and say, OK, we get it, but let us figure out how to do this right because we think labs developing tests is a good thing. We are not here to stop that, we are here to try to have that balance between the development of new tests, but also tests that work, making sure it is safe and effective, because there is no value to doctors and patients if the test doesn't work. That hurts people and that is a cost on our health care system.

Mr. BILIRAKIS. How many labs would suddenly fall under the FDA authority under the proposed guidance?

Dr. SHUREN. In part, we will see that with notification. We are estimating that that number—we know for the labs who can make LDTs, who are allowed to, according to CMS that number is 6,000, but not all of them make LDTs. That number is much smaller. And we think a number of these LDTs are also subject to the continued enforcement discretion. So for some of these labs that are making tests that, again, they are not coming in the door for us.

Mr. BILIRAKIS. I believe this was mentioned earlier, but I will ask the question again. I have heard concerns that some of the guidance that FDA issues may be duplicative or contradictory with the requirements under CLIA. Will FDA ensure that its guidance will harmonize with the current regulations required under CLIA?

Dr. SHUREN. Yes, and in developing our framework and other materials, we have been coordinating with CMS. Our goal is not to be duplicative.

Mr. BILIRAKIS. Thank you very much.

I yield back, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman.

And now recognizes the ranking member of the full committee, the gentleman from California, Mr. Waxman, 5 minutes for questions.

Mr. WAXMAN. Well, thank you very much, Mr. Chairman.

Dr. Shuren, one of the themes of the 21st Century Cures Initiative has been that advances in molecular medicine and information technology will enable the use of smaller, more efficient clinical trials and faster development of new cures. For those improvements to be realized, we will need to rely on increasingly sophisticated tests that can both accurately analyze the genetic and molecular properties of diseases as expressed in individuals, and recommend treatment regimens based on those analyses. Thus, these sophisticated tests appear to be central to what the 21st Century Cures Initiatives is all about.

Could you describe for us the kind of genomic and other sophisticated tests that are in existence or under development that are aimed at helping to guide clinical decisions, and can you tell us what role they play or hope to play in developing and improving treatments, and can you explain what FDA's role is or will be in their development and use?

Dr. SHUREN. OK. So increasingly, we are seeing tests to identify those patients who would benefit from particular therapies and those who would not, so that you are not giving a treatment and exposing that person to side-effects when they are not going to get a benefit in return. And we see this a lot in cancer, we are seeing it in some other fields as well.

Getting the right treatment to the right patient depends upon having accurate and reliable test results. If they are not, that is where mistakes happen, and that is what has happened with people who didn't get treatment who should. So tests that were there for breast cancer had high false negatives, so people were being told the treatment that is available, you are not a candidate for, when, in fact, they would have been a candidate. We heard earlier about Oversure where one of the treatments is having surgery because if you have ovarian cancer, have it taken out. And you had examples where a woman didn't have cancer, had the surgery, woman who had cancer told not, didn't have the treatment when they should have had treatment at that point. And we see it even in heart disease. So there is a case of a test for risk of heart disease, and then the use of statins—responsive to statins. Well, it turns out—we wound up seeing the data on this, and there was a subsequent study that showed these markers didn't actually predict it. The test was not valid, didn't do it, but at the time when that data was there, over 150,000 people got tested. We estimate the cost may be over \$2 billion. Even Eric Topol, who many of you were talking about with personalized medicine and some of the work there, he actually talked about that this was a great example. Going forward, this story should serve as a valuable reminder of the potential pitfalls present in prematurely adopting a genomic test without sufficient evidence.

Mr. WAXMAN. Well, on the next panel, Mr. Mertz, from the American Clinical Lab Association, will testify that if there were problems with LDTs, we would have more publicity about them. He cites a 2008 statement by the Advisory Committee on Genetics, Health and Society that there have been few documented cases in which patients experienced harm because of errors in a CLIA-regulated genetic test.

Do you agree with that, would doctors and patients necessarily know if tests weren't giving good advice for clinical decisions? Your testimony mentions some of these, but please describe any examples of the risks or harms of LDTs that have led FDA to change its enforcement policy in this area.

Dr. SHUREN. Yes. So doctors and patients wouldn't know. I mean you order a test, you don't know it is FDA approved or it is not FDA approved. That is the state of affairs. And so you don't know if you have those guarantees or not. That is the way things are today. And of course you are relying on those test results then for making a decision on how to care for the patient.

Mr. WAXMAN. Well, CLIA regulates the labs. If CLIA regulates the labs, should we rest assured that the tests from that lab will be accurate?

Dr. SHUREN. No. CLIA's purpose is not to assure the tests are safe and effective. CMS recognizes that too and has noted distinctions between what FDA does and what CMS does. They are com-

plementary systems, and in going forward, we need to make sure we are coordinated and we avoid any duplication, but they are complementary systems. And the Secretary's Advisory Committee did note, yes, there were a few reports of problems because there isn't a system there for identifying those problems. That is one of the things that we would put in place, but that same committee, that same Advisory Council, also said the absence of evidence doesn't mean that there is an absence of a problem. And, in fact, they came back and said we recommend the FDA begin enforcing requirements for LDTs. That was their conclusion.

Mr. WAXMAN. So even though we know it is a decent lab, they live up with the good standards, we don't know if the result of the test is going to be accurate in helping the patients or not?

Dr. SHUREN. Right. We have for—

Mr. WAXMAN. May even do them harm.

Dr. SHUREN. Right, and we had for H1N1, so when that came out, by the way, the original samples came from China. Only the CDC had them. And then when the emergency was declared, CDC had developed a test and we gave them an EUA within days. Then they made the samples available to other labs. The labs who developed things beforehand had no access to the H1N1 samples, and then they came in the door. Now, we cleared—we gave EUA authority to some of the labs—

Mr. WAXMAN. EUA is—

Dr. SHUREN [continuing]. But some of them—

Mr. WAXMAN. EUA is?

Dr. SHUREN. I am sorry, emergency use authorization, in the setting of that pandemic. But some of the labs, their data and from pretty prestigious academic institutions, their tests were problematic. And we saw the data, that is how we know, and then they weren't out there on the market. That is what FDA does, but again, we are trying to strike that right balance in innovation, access, and safety and effectiveness.

Mr. WAXMAN. Thank you.

Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman.

And now recognizes the vice chairman of the full committee, the gentlelady from Tennessee, Mrs. Blackburn, 5 minutes for questions.

Mrs. BLACKBURN. Thank you, Mr. Chairman. And I appreciate the emphasis that we have on 21st Century Cures, and the opportunity for all of us to visit with you, Dr. Shuren, and we thank you for your time and for being willing to come over here and talk with us and answer the questions. I think that we are all interested in solving access issues for our constituents, and part of that being preserving access to affordable health care for all Americans. And right now the cost of health care seems to be going through the roof, and we hear about it every day.

Let us go back and talk a little bit about the guidance document. I know Mrs. Ellmers and Mr. Bilirakis have both touched on it with you, and when you are looking at the guidance document and the LDT issue, you know that there could be numerous requirements that could be put in place from your guidance document. We

know that you all contend that guidance documents are not binding on the industry.

Now, when we are out there talking with some of our innovators, and talking with those that are trying to work through the process with you all, what we hear is, well, they might not do something, but they could, and the uncertainty that exists in that. So how do you, as we talk about answering the questions for constituents, how do you reconcile that difference, you might not but you could, and the guidance documents aren't binding? So how do you reconcile that?

Dr. SHUREN. So just to flip around in this case, here we are talking about the requirements to comply with the Food, Drug, and Cosmetic Act are already in place for the labs. We have chosen not to enforce those requirements. We haven't taken action for the people who aren't meeting it, for the most part, but that is the change that we are making. So unlike in other cases where we are imposing a requirement, we are reinterpreting that requirement under the law, we are not doing that here, we are simply withdrawing enforcement discretion, saying here are the requirements, they are already on the books, there are regulations about them, some cases there are guidances, and you would meet that just like you would as a conventional manufacturer, but we maintain enforcement discretion still in some cases where we say these particular requirements, as outlined here, you don't have to comply with, we will not enforce those.

Mrs. BLACKBURN. Yes, and I appreciate that and I appreciated your comments about the medical device tax, and you and I have talked about the Software Act and the medical apps that are there, but I just want to highlight with you again that sometimes that discretion, that uncertainty is very difficult for many that are innovating in that space because they know you might not do something, you probably won't do something right now, but it doesn't state what you are going to do if you change your mind. And as they look at federal agencies, you all included, mission creep is something that is—that they are concerned about, and also lack of economic analysis. So I would just—I would highlight that to you.

Let me go back to something Mr. Griffith raised earlier. In addition to Section 807.65(i) of the federal regulations which specifically list clinical labs as a class of entity that is exempt from establishment, registration, and device listing, the preamble to these final regulations implementing the registration requirement unequivocally emphasizes this point in stating the commissioner believes that full-service labs and similar establishments are exempted from registration. Were you aware of these regulatory provisions currently on the books?

Dr. SHUREN. Yes, so this provision pertains to labs when they are using tests. It does not pertain to when they are manufacturing—

Mrs. BLACKBURN. OK.

Dr. SHUREN [continuing]. Tests. That is the distinction. And I am also sympathetic, I understand the predictability when people say, well, if you put a policy in place, and here people are saying when you exercise enforcement discretion, what about, you could take it away tomorrow. This should be a poster child about our taking

away enforcement discretion. We have been at it for years. I was a very young man when this started back in the 1990s. I now have gray hair. So it does not happen overnight. In some respects, I hate to say it, I wish it would. I would probably not have the gray hair.

Mrs. BLACKBURN. Well, I think we all end up having gray hair. It is one of the blessings that comes our way from being able to solve problems and work through issues that affect all Americans, and we look for a good resolution to those, and I hope that you are going to commit to work with us on the software component, the medical apps and keeping these free of the medical device tax. We have got a lot of people that are looking to expand access, and that is a good way to do it.

I yield back.

Mr. PITTS. The chair thanks the gentlelady.

Now the chair recognizes the gentlelady from California, Ms. Eshoo, 5 minutes for questions.

Ms. ESHOO. Thank you, Mr. Chairman. I appreciate the legislative courtesy. While no longer a member of this subcommittee, the committee rules do allow members of the full committee to participate, and I appreciate it.

I have a statement that I would like to submit for the record, and ask unanimous consent to do so.

Mr. PITTS. I am sorry, I didn't hear you.

Ms. ESHOO. Yes, I just ask—

Mr. PITTS. I am trying to get those—

Ms. ESHOO. You mean you weren't paying—

Mr. PITTS [continuing]. Klieg lights turned off.

Ms. ESHOO. You weren't paying attention to me, Mr. Chairman. No, I just asked unanimous consent to produce a statement into the record today.

Mr. PITTS. Without objection—

Ms. ESHOO. Thank you very much.

Mr. PITTS [continuing]. So ordered.

[The prepared statement of Ms. Eshoo follows:]

PREPARED STATEMENT OF HON. ANNA G. ESHOO

Mr. Chairman, thank you for holding this hearing today to examine the regulation of laboratory developed tests (LDTs). I appreciate the opportunity to learn more about this issue and to hear from the FDA and from stakeholders about how the agency's proposed changes will affect patients, doctors, and health care innovation.

The FDA's primary mission is to ensure that drugs and devices are safe and effective. Diagnostics are a critical part of our health care ecosystem, helping doctors target what's wrong with a patient so that they can be treated with the utmost precision, focusing on the necessary therapies while reducing unnecessary interventions.

While the FDA regulates some diagnostics, many are never reviewed by the agency. This is because our bifurcated regulation of diagnostics means that the FDA regulates diagnostics developed as "kits" while CMS regulates LDTs under the Clinical Laboratory Improvements Act (CLIA). The FDA has the authority to regulate LDTs but until now, has exercised regulatory discretion in allowing these tests to be regulated solely by CLIA.

As diagnostics become more complex and lead to greater clinical decision making, it's important that they receive increased scrutiny to protect patient safety. FDA's proposal to fundamentally change the regulatory paradigm for LDTs can lead us in the right direction, but the new regulations must be implemented in a way that furthers innovation and the development of personalized medicine.

Ms. ESHOO. Dr. Shuren, it is good to see you, as always.

I think the benefit of sitting here and listening to all the questions and your responses is the following. When I go to either Stanford University or the Palo Alto Medical Foundation, part of all of these exams, and if there need to be further examination of things, are tests. I want my tests to be accurate. I want my tests to be accurate, and I think every single one of us do too. And I think that we are at a juncture today where we should be celebrating something, and that is that there has been so much innovation that has moved forward relative to diagnostics, they are far more sophisticated, we have a broader and greater capacity to make determinations relative to diseases that were at one time a death sentence and today can be manageable if, in fact, there is a correct diagnosis. And so these tests are really central in all of our lives, and I think that, speaking for myself, the older I get, I can't wait for the results of the tests to come back to know that everything is all right, but we depend on accuracy. And I think that the FDA, in terms of its role, a key role is to ensure safety and efficacy of drugs and devices.

This is really more of discussion of how this is going to work. I know that there is a question that has been raised about whether the Agency has the authority. It seems to me that you do. My concern is that this be done in a very smooth and fair way because if in moving through this process, I want to ask you why it is 9 years. I mean a lot of things can happen in 9 years. I mean can't you do something in a shorter period of time so that the stakeholders have predictability and know what the rules of the game are going to be? That is one of my questions. I know that this was stuck at OMB for a long time, and I am very curious to know what all of a sudden loosened this up, so that OMB changed its mind. What was it that concerned them that held it up for so long, and what is it that put them in a better mood and gave you the hand signal to move on? And what would you say to the stakeholders, because I have listened to many of them, I don't have the answer, but I have listened to many of them about the effects of the proposed changes and what is burdensome, what isn't, what would you say to them about innovation not being damaged as we move forward to protect the efficacy and the safety that I spoke to both as a member representing 700,000 people and as a patient, as an individual?

Dr. SHUREN. So phase-in for 9 years, we picked that number for a couple of reasons. One, we wanted to give labs time to better understand what requirements were, we wanted to have a process to also classify—

Ms. ESHOO. But may I—

Dr. SHUREN [continuing]. The tests—

Ms. ESHOO. I just want to interject something. If it is going to take 9 years to understand something, I don't think that sends the right signal, honestly, because it—then it must be so enormously complex that it is going to take almost a decade for people to figure out, so it doesn't seem like it is a source of comfort to me. Now, maybe it is the flipside. Maybe that is a comfortable zone for people, that they want to take it very, very, very slowly, but if your assumption is that it is going to take 9 years for people to under-

stand something, that, to me, suggests some kind of complexity that is deep and broad.

Dr. SHUREN. Yes, and if people are looking for faster, that is a conversation to have. It is a risk-based phase-in, so the highest risk ones we bring in first. There are a lot of tests out there that the risk classification hasn't been determined yet, so we need time for the public process and expert panels to look at that when we get notification of tests, and then we want to fold this in with the resources we have so we are able to manage reviews in a way that doesn't overtax the system that we have. So that is how we came up with the 9 years.

Ms. ESHOO. Yes.

Dr. SHUREN. As to OMB, what I can say is a higher authority weighed in and we are moving authority. It sounds like Hebrew National Hot Dogs.

Ms. ESHOO. Higher—it does. I was going to say it sounds like an ad. Yes.

Dr. SHUREN. Yes.

Ms. ESHOO. Yes.

Dr. SHUREN. And then in terms of, with innovation, one thing I will say is innovation isn't just something new—

Ms. ESHOO. Yes.

Dr. SHUREN [continuing]. It is also valuable—

Ms. ESHOO. Yes.

Dr. SHUREN [continuing]. To patients. If you have an innovative test, doesn't matter if it is new, it has to be safe and effective otherwise we are not doing service by patients, and then it isn't real innovation.

Ms. ESHOO. Yes.

Dr. SHUREN. Newness for the sake of newness isn't good, and spending our health care dollars just because it is new but it may not work is a fool's errand.

Ms. ESHOO. Yes.

Dr. SHUREN. So how do we strike that balance on innovation—

Ms. ESHOO. Yes.

Dr. SHUREN [continuing]. And safety and effectiveness. That is the dialogue we are trying to have. We put something out, at least now people can react to it and have a much more structured conversation.

Ms. ESHOO. Thank you, Dr. Shuren.

Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentlelady.

That completes the round of questioning. We have one follow-up per side. Dr. Burgess, you are recognized 5 minutes for follow-up.

Mr. BURGESS. Mr. Chairman, I just really, really like to know the higher authority at OMB, because you and I talked about this at the end of July when you called me and said, OK, I am exercising the 60-day requirement, and my question went to the economic impact and the questions such as Ms. Eshoo asked at OMB. These are valid questions and, to the best of my knowledge, you have not answered those. You didn't answer it in July, you haven't answered it today, so what was the deal at OMB with assessing the economic impact, or, in fact, are we proceeding on this where we really have no earthly idea as to the economic impact?

Dr. SHUREN. Well, so two different things. I guess the question originally was the holdup at OMB, the holdup wasn't overdoing an economic analysis on this. They had—

Mr. BURGESS. Is that not part of OMB's job to look at the economic impact of changes made by the agencies—

Dr. SHUREN. They—

Mr. BURGESS [continuing]. Just as a general rule?

Dr. SHUREN. They do that in rulemaking for certain rules when they review those.

Mr. BURGESS. Is that why we avoided rulemaking in this instance?

Dr. SHUREN. No, because this is enforcement policy and we do that with guidance. We have done that historically with guidance. There is nothing different here, and, in fact, as I mentioned, we came out with guidance in—7 years ago—

Mr. BURGESS. OK, well—

Dr. SHUREN [continuing]. In 2007.

Mr. BURGESS. But back to the question of the economic impact.

Dr. SHUREN. Yes.

Mr. BURGESS. Do we, as we sit here today, do we have any idea as to the economic impact of this guidance that you are proposing?

Dr. SHUREN. I do not have hard numbers to share with you. And in part, some of this if you want to look at it is when we have the lay of the land for those labs that would have to come in the door and be subject. Part of it too is what will the final framework be. This is starting a dialogue so we can have that discussion about what the final policy will look like. And then lastly, as I mentioned before, labs are supposed to validate their tests. They are supposed to do the studies. As people said, hey, it is expensive to do studies. They are supposed to do that. So if they have done it, the cost to them is, in certain cases they would be sending it to us so we can review that.

Mr. BURGESS. Thank you, Mr. Chairman. I will yield back.

Mr. PITTS. The Chair thanks the gentleman.

I now recognize the gentleman, Mr. Pallone, 5 minutes for follow-up.

Mr. PALLONE. Thank you, Mr. Chairman.

The ACLA claims that once a manufacturer gets a test approved, it never improves it because of fear of needing new approval. And they give the example of an HIV Western Blot Kit not having significant improvement since first one was approved in the '80s, and the first kit to be approved by FDA was 2 years after the first LDT test was used without FDA approval. And ACLA also gives the example of a lab making improvements to an FDA-approved test kit, and says that the approach under the guidance of requiring labs to seek FDA approval for such activities is unreasonable, and encroachment on the practice of medicine and a disincentive that will limit patient access to cutting-edge diagnostics.

So I just wanted to know how would you respond to that claim?

Dr. SHUREN. Well, so test developers do improve their tests, and I turn to the people representing that community to maybe address that on the next panel, but yes, they do come back and they do improve their tests. In the setting where there wasn't a test available, one of the things we have in our framework is an LDT for an

unmet need where there is no approved or cleared test to allow then labs in certain circumstances to have that test, have it out there and not go through FDA review, but then when a company comes in and they make the test for the same intended use, now we have an FDA-approved test, we have seen the data, we know it is safe and effective, that is the time for the other lab to say I either want to bring in my test and share the data, or I will use the FDA-approved test. And then if they want to improve a test or they want to make a better test, then have the data to support it because we have seen where you make a claim it is better but is it really a better test, because you are telling doctors it is a better test, so use my test because it is better than the one the FDA approved. Well, how do doctors know that? That is what we are here for, to try to make those assurances if you are truly making it better. And we have seen sometimes you claim a test is better, you add other markers on, but it turns out you haven't shown those markers actually better inform the diagnosis. But you should do that.

Mr. PALLONE. All right, thanks. I think we need to achieve the right balance, but I appreciate it.

Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman.

That concludes the questions of the committee at this time. We will have follow-up questions for you that we will send. We ask you please respond promptly. And thank you for your patience and responsiveness this morning.

This concludes the first panel. We will take a 3-minute recess as the staff sets up the second panel.

[Recess.]

Mr. PITTS. The subcommittee will reconvene. We will ask everyone to please take their seats, and ask the witnesses to please take their seat at the table. Please take your seats. I would like unanimous consent to submit the following for today's hearing record: Comments of the Small Biotechnology Business Coalition; a statement from the Association for Molecular Pathology; a letter from Randy Scott, Chairman, CEO of InVita Corporation in San Francisco; and a letter from the American Association of Bioanalysts, the AAB, and the National Independent Laboratory Association, NILA, representing independent community and regional clinical laboratories.

Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. PITTS. On our second panel today we welcome each of you, and I will introduce the panel in the order of their presentations. First, Mr. Andrew Fish, Executive Director, AdvaMed Diagnostics; then Dr. Kathleen Behrens Wilsey, Co-Founder of Coalition for 21st Century Medicine; Mr. Alan Mertz, President, American Clinical Laboratory Association; Dr. Christopher Newton-Cheh, Assistant Professor of Medicine, Harvard Medical School, and Cardiologist, Massachusetts General Hospital, testifying on behalf of the American Heart Association; and finally, Dr. Charles Sawyers, Immediate-Past President, American Association for Cancer Research.

Thank you all for coming. Your written testimony will be made a part of the record. You will be each given 5 minutes to summarize your testimony.

And, Mr. Fish, we will start with you. You are recognized for 5 minutes.

STATEMENTS OF ANDREW FISH, EXECUTIVE DIRECTOR, ADVAMED DIAGNOSTICS; KATHLEEN BEHRENS WILSEY, PH.D., CO-FOUNDER, COALITION FOR 21ST CENTURY MEDICINE; ALAN MERTZ, PRESIDENT, AMERICAN CLINICAL LABORATORY ASSOCIATION; CHRISTOPHER NEWTON-CHEH, M.D., ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, CARDIOLOGIST, MASSACHUSETTS GENERAL HOSPITAL; AND CHARLES SAWYERS, M.D., IMMEDIATE-PAST PRESIDENT, AMERICAN ASSOCIATION FOR CANCER RESEARCH

STATEMENT OF ANDREW FISH

Mr. FISH. Thank you, Chairman Pitts, Ranking member Pallone, and Members of the subcommittee, for the invitation to testify at today's hearing. My name is Andrew Fish, and I am the Executive Director of AdvaMed Dx, the trade association representing the leading manufacturers of medical diagnostic tests. I have submitted a longer statement for the record, and will summarize key points for you this morning.

AdvaMed Dx member companies develop FDA-cleared diagnostic tests for use in a wide range of health care settings, not only in clinical laboratories, but also in numerous point-of-care environments, including emergency rooms, doctors' offices, clinics, and even in the home.

Whether developing a rapid molecular test for flu or TB, an implantable blood glucose monitor that interfaces with a smartphone, advanced genetic tests designed to guide use of specific cancer drugs, or the first FDA-approved platform for high-speed gene sequencing, diagnostic manufacturers are proud to wear the mantle of innovation in this critical area of health care.

AdvaMed and AdvaMed Dx have been pleased to work closely with the Energy and Commerce Committee on many issues related to FDA regulation of medical devices and diagnostics, and appreciates the committee's continued leadership.

The questions before the committee today are whether and how laboratory-developed tests or LDTs should be regulated to assure their safety and effectiveness. Three essential points support our conclusion that FDA should regulate LDTs under a risk-based approach. First, LDTs are diagnostic tests, and all diagnostics present the same patient risks, regardless of whether they are developed by a manufacturer or a laboratory. Second, the LDT market has changed dramatically in recent years to encompass even the most advanced, complex, and high-risk tests, and under our current oversight paradigm, LDTs are not reviewed for safety and effectiveness, when the same tests made by a manufacturer are subject to FDA clearance or approval. Third, existing statute and FDA regulation already encompass LDTs, and FDA's decision to enforce those regulations with respect to LDTs is an appropriate policy de-

cision by the only agency with the authority, expertise, and infrastructure necessary to assure the safety and effectiveness of diagnostics.

We have spoken earlier in this hearing about CMS's authorities over laboratories under CLIA. CMS itself as the agency that implements CLIA has made it clear that CLIA does not duplicate FDA regulation. FDA regulation encompasses numerous elements that were never intended to be covered by CLIA, including premarket review and assurance of clinical validity. It makes no sense to create a new set of authorities at CMS when FDA has a well-developed regulatory system and infrastructure that already encompasses LDTs.

For years, stakeholders have recognized the inadequacy of current oversight of LDTs, and have called for FDA to enforce existing regulations that apply to LDTs, just as they do to all other diagnostics. I submitted a document noting comments from a variety of stakeholders supporting FDA action on LDTs, and ask that it be included in the record.

The current diagnostics oversight paradigm results in a tremendous public health gap, and highly disparate treatment of tests that are the same from the perspective of patient risk and safety, simply on the basis of whether they are developed by a manufacturer or a laboratory. This is bad public policy, provides an opportunity to use tests in a clinical setting that have insufficient clinical data, and stifles investment in high-quality products that are assured safe and effective for patients.

We see these challenges arise, for example, when, shortly following an FDA approval of a pharmaceutical, along with its companion diagnostic, laboratories advertise that they can perform an LDT version of that diagnostic test.

It is important to note that the threshold question of whether LDTs should be regulated by FDA turns first and foremost on patient safety. From this perspective, we believe that FDA oversight of LDTs is necessary. While FDA regulation is not without challenges for our industry, we have worked constructively with the Agency on various improvements to its regulation of diagnostics, and are pleased with significant progress, including increased use exemptions and a new triage program to speed reviews. We look forward to continuing to work with this committee on ways to help improve FDA oversight.

The risk-based approach to LDT regulation that FDA has set forth addresses current gaps in LDT oversight by focusing Agency resources on tests that pose the highest risk to patients. At the same time, FDA appropriately recognizes the important role that LDTs can play in providing care to patients in the medical institution setting, and explicitly preserves the ability of laboratories in those settings to continue innovating in the area of LDTs. AdvaMed Dx commends FDA for moving forward to address the patient safety gaps that currently exist in LDT oversight, and supports the key elements of the oversight framework that FDA recently announced.

Again, thank you for the opportunity to speak to this important issue at today's hearing.

[The prepared statement of Mr. Fish follows:]



AdvaMedDx
Advancing the Future of Diagnostic Testing

AdvaMedDx

Written Testimony

U.S. House Energy & Commerce Committee
Subcommittee on Health

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

September 9, 2014

Thank you, Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee for the invitation to testify at today's hearing. My name is Andrew Fish, and I am the executive director of AdvaMedDx, the trade association representing the leading manufacturers of medical diagnostic tests. AdvaMedDx operates as a division of AdvaMed, the medical device manufacturers trade association, under the leadership of a separate board of directors.

AdvaMedDx appreciates the opportunity to submit testimony on the important topic of regulation of laboratory developed tests (LDTs). First, I will describe how current gaps in our regulatory system lead to different treatment of diagnostic tests, depending solely on whether the test is developed by a manufacturer or a laboratory and without regard to patient safety. Second, I will explain how rapid changes in the complexity, risk, and marketing of LDTs have created an imperative for new LDT oversight. Finally, I will summarize FDA's recent proposed framework for LDT oversight and note support for FDA action from a wide variety of stakeholders, including AdvaMedDx and our member companies.

Medical diagnostic tests, often referred to as *in vitro* diagnostic, are tests performed on specimens taken from the body, such as blood, urine, saliva, or tissue. These diagnostic tests are a cornerstone of the modern health care system, providing critical

information at every stage of care: screening, diagnosis, prognosis, treatment guidance, and health monitoring.

There are thousands of different diagnostics in use and billions of individual tests are performed in the United States each year, spanning many different technologies and providing essential information about a wide range of diseases and health conditions.

Molecular diagnostics is one area of diagnostics in which rapid advances are being made and also is a major factor in FDA's decision to enforce existing regulations for LDTs. Molecular diagnostic tests detect target proteins and specific genetic sequences ("biomarkers") to help identify disease presence, type, progression, and recurrence risk. These diagnostic tests help clinicians tailor care to subpopulations and individuals—enabling targeted "personalized", or "precision", medicine. An important component of personalized medicine is the emerging field of companion diagnostics, in which a molecular diagnostic test is used to identify whether a specific drug (for which the test is a companion) is right for an individual patient.

The diagnostics developed and distributed by AdvaMedDx member companies – including advanced molecular diagnostics – are used in a variety of health care settings, including laboratories, hospitals, doctors' offices, clinics, and the home. Diagnostics represent only about 2 percent of health care spending but influence at least 60-70 percent of health care decisions.

Summary Points

- For years, stakeholders have recognized the inadequacy of current oversight of LDTs and called for FDA to enforce existing regulations that apply to LDTs just as they do to all other diagnostics. A document is attached (Attachment A) to this testimony that notes comments from a variety of stakeholders supporting FDA action on LDTs.

- Under existing statute, medical devices include diagnostic tests. Consequently, all diagnostics—regardless of who develops them—are subject to FDA regulation for assurance of safety and effectiveness.
- In an exercise of enforcement discretion, however, FDA has long declined to enforce its diagnostics regulations with respect to LDTs because they historically were considered low risk. This means that FDA is not reviewing LDTs for safety and effectiveness and LDTs are not subject to numerous other aspects of FDA regulation designed to protect patients.
- Over time, FDA's exercise of enforcement discretion for LDTs has become recognized by many stakeholders, as well as FDA, as a clear gap in diagnostics oversight. As diagnostics technologies and the laboratory business have evolved, even the most advanced tests – such as technically complex genetic tests that guide choices among cancer treatments – are now developed and offered by laboratories as LDTs.
- Laboratories are regulated by the Centers for Medicare and Medicaid Services (CMS) under CLIA – the Clinical Laboratory Improvement Amendments of 1988. As CMS itself has made clear, CLIA regulations are not a substitute for FDA oversight. Many critical features of FDA oversight are missing from CLIA. Furthermore, CMS does not have the expertise or resources to oversee LDTs in the same manner as FDA.
- Unlike FDA oversight of diagnostics, CLIA:
 - Does not regulate the safety and effectiveness of diagnostic tests;
 - Does not require pre-market review of tests;
 - Does not require demonstration of clinical validity (whether the test is meaningful for clinical decision making);
 - Does not require systematic adverse event reporting;
 - Does not have a process for corrections or recalls.

- A test is a test—and presents the same risk for patients regardless of whether it is developed by a manufacturer or a laboratory. Potential harms to patients whose tests return incorrect results include unnecessary treatments, with their accompanying costs and side effects, and treatment delay or failure to obtain appropriate treatment, all of which lead to worse outcomes for those patients.
- Maintaining two very different oversight mechanisms for tests that are the same from the perspective of patient safety is bad public policy, provides an opportunity to use tests in clinical settings without sufficient clinical data, and stifles investment in high quality products that can stand up to FDA review.
- The risk-based approach to LDT regulation that FDA has set forth addresses current gaps in LDT oversight by focusing agency resources on tests that pose the highest risk to patients. At the same time, FDA appropriately recognizes the important role that LDTs can play in providing care to patients in the medical institution setting and explicitly preserves the ability of laboratories in those settings to continue innovating in the area of LDTs.

Diagnostics Regulation and Gaps in Oversight of LDTs

LDTs Subject to FDA Oversight

The 1976 Medical Device Amendments require FDA to review the safety and effectiveness of all medical devices, specifically including diagnostic tests as defined in section 210(h) of the Federal Food, Drug, and Cosmetic Act (FDCA). As a category of diagnostics, LDTs—which are tests developed solely by a laboratory for use only within that laboratory—are subject to the provisions of the FDCA and FDA regulation that require assurance of safety and effectiveness for diagnostics.

To date, however, FDA has exercised enforcement discretion for LDTs, meaning that

FDA has not enforced applicable regulations with respect to these tests and has not been reviewing LDTs to assure safety and effectiveness. LDTs also have not been subject to numerous other aspects of FDA regulation that are designed to protect patients.

How FDA Regulates Diagnostics

The main elements in FDA's review of diagnostics are analytical and clinical validity. *Analytical validity* refers to the accuracy of a test in detecting the specific characteristics that it was designed to detect – for example, the presence or absence of a particular gene or genetic change. This is often measured by sensitivity, specificity, detection, precision, and repeatability. Sensitivity refers to how often the test is positive when the target is present, and specificity refers to how often the test is negative when a target is not present. *Clinical validity* refers to how well the target being analyzed is related to the presence, absence or risk of a specific disease or disorder. This is often measured by sensitivity and specificity. Sensitivity refers to how often the test is positive when the disorder is present, and specificity is how often the test is negative when the disorder is not present.

Assurance of both analytical and clinical validity is essential to patient safety. Under the current oversight paradigm, there is little or no transparency for doctors and patients regarding whether tests performed are FDA cleared or are unapproved LDTs, and to what extent there is adequate clinical validity data supporting the use of an LDT to make a clinical diagnosis.

CMS Oversight of LDTs is Not a Substitute for FDA

Laboratories are regulated by CMS under CLIA – the Clinical Laboratory Improvement Amendments of 1988. CMS itself has acknowledged the clear differences between CLIA oversight of laboratories and FDA oversight of diagnostic tests, noting FDA's unique role, scope, and qualification to assure the safety and effectiveness of tests.

CLIA regulations focus on lab practices, including testing procedures, certification, and personnel. CLIA regulations do not regulate the safety and effectiveness of tests and are not a substitute for FDA oversight. Critical features of FDA oversight are not covered under the CLIA program, which regulates good lab practices and is required for all labs performing tests, including both FDA approved/cleared tests and LDTs. Furthermore, CMS does not have the expertise or resources to oversee LDTs in the same manner as FDA.

Unlike FDA oversight of diagnostics, CLIA:

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

Growing Use of More Complex and High-Risk LDTs without FDA Oversight

FDA chose to exercise enforcement discretion for LDTs because historically they were typically lower risk tests with well-established test methods or used in low volume. Now, however, LDTs regularly developed and offered by laboratories encompass even the most complex and advanced molecular diagnostics – such as genetic tests that guide choices among cancer treatments or tests used in the diagnosis and treatment of common and serious or life threatening disorders. This is true not only of well-established laboratories, but also of new companies that establish themselves as laboratories in order to offer new tests without having to face scrutiny by FDA.

The American Society for Clinical Pathology (ASCP), in 2010, summarized the challenges posed by the evolution of LDTs as follows.

"LDTs, initially used to diagnose rare diseases and conditions, were intended to be used within a single institution by physicians and pathologists actively engaged in their patients' care. In recent years, LDTs have become increasingly more complex, and their use has expanded to assess high-risk, but relatively common diseases and conditions. However, as LDTs have begun to assume a more pivotal role in medical decision-making, they are more frequently being performed in geographically distant commercial laboratories instead of within the patient's health care setting under the supervision of a pathologist and treating clinician. In some instances, LDTs are being marketed directly to the patients. ASCP is concerned that due to the increased application of LDTs for genetic testing and personalized medicine, the use of LDTs outside of the physician-patient context, and the development of LDTs by larger corporations, that some LDTs may not have been properly validated for their intended use, putting patients at risk for missed diagnosis, wrong diagnosis, and inappropriate treatment."¹

The types of trends and concerns that ASCP characterized in 2010 have continued, especially with regard to genetic testing, and have likely accelerated due to an ever growing body of research suggesting biomarker-disease correlations and technology improvements and cost decreases in genetic testing.

It also is observed that laboratories promote their LDTs to a national marketplace. Specifically in the area of companion diagnostics, we understand that shortly following FDA approvals of a pharmaceutical along with its companion diagnostic, laboratories often advertise that they can perform an LDT version of that diagnostic test. While the drug is labeled to indicate use of the diagnostic to assess whether the drug is appropriate for a particular patient, an LDT version of the diagnostic is not reviewed by FDA and may have different performance characteristics or even use different technology than the companion diagnostic approved by FDA. Marketing these LDTs as companion diagnostics without FDA assurance of safety and effectiveness does not serve the public health.

¹ *Policy Statement, Regulation of Laboratory Developed Tests* (Policy Number 10-02), American Society for Clinical Pathology, 2010.

Specific numbers on the development and use of LDTs are difficult to obtain because there is no required reporting of this information. Patient billing records also do not yield this information because there is no widespread billing mechanism for identifying whether the test used was FDA-cleared or an unapproved LDT. (There are initiatives using test-specific identifiers that ultimately may bring more transparency to LDT usage through payment records, but these are only in early stages.)

As of September 5, 2014, the voluntary Genetic Test Registry maintained by the National Center for Biotechnology Information listed 8,245 clinical tests in the U.S. (meaning the tests are being used for diagnostic purposes, as opposed to solely for research). While reporting FDA status for those tests is voluntary, just 15 of those tests report FDA approved/cleared status. Of the remainder, 1,072 tests report that they are used pursuant to FDA enforcement discretion, and there is no information regarding FDA status for the remaining 7,158. Of those tests not reporting FDA status, however, they are unlikely to be FDA approved/cleared.² Analysis of the GTR shows that the number of tests in the database has grown sharply in recent years.

FDA Must Enforce Diagnostics Regulation for LDTs

A test is a test – and presents the same risk for patients regardless of who makes it. Potential harms to patients and public health from tests that return incorrect results include unnecessary treatments with accompanying costs and side effects, treatment delay or failure to obtain appropriate treatment, unnecessary surgery, overuse of antibiotics, and overall worse outcomes than patients who received correct results.

Without further action by FDA, the current regulatory system leaves critical gaps with respect to patient safety and public health regarding the use of LDTs. A number of examples have been noted by FDA and other commentators, including the Institute of

² Information reported from the National Center for Biotechnology Information based on tests listed in the Genetic Test Registry (<http://www.ncbi.nlm.nih.gov/gtr>).

Medicine and the Centers for Disease Prevention and Control, in which insufficient clinical validation led to either harm or unacceptable risk of harm that could have been precluded by FDA review.

Just as important, the lack of comprehensive registration and listing of LDTs and mandatory adverse event reporting means that FDA, doctors, and patients alike have insufficient information to understand either the range of LDTs that are being used—and, in many cases, marketed to doctors and patients—without FDA review, or the extent to which LDTs are being used without appropriate clinical validation and consequently failing to perform as expected or advertised.

Merits of FDA's Proposed LDT Oversight Framework

The Food and Drug Administration (FDA) has announced that it will modernize its regulation of diagnostic tests by requiring premarket review for moderate and high risk laboratory developed tests (LDTs).

While AdvaMedDx expects to provide more detailed comments on FDA's anticipated draft guidance on LDT regulation, we commend FDA's commitment to the thoughtful development of a risk-based LDTs oversight framework. We note key elements of the framework, including (1) a risk-based approach, phased in over a multi-year time frame; (2) notification by laboratories to ensure a transparency and comprehensive public registration of LDTs in clinical use; (3) requirements for adverse event reporting; and (4) continued use of enforcement discretion for certain types of LDTs to minimize disruption to the laboratory industry and ensure continued innovation. The approach also works to support continuity in tests, particularly in rare disease and healthcare institution laboratories testing, consistent with risk based approach.

Risk-Based Approach

AdvaMedDx has long called for FDA to modernize its regulation by ensuring risk-based regulation of all diagnostics. In its proposed framework, FDA has indicated that it will take a risk-based, phased-in approach that focuses the agency's resources on tests that pose the highest risk to patients. FDA plans to phase in this oversight over a minimum of nine years following finalization of the LDTs guidance that is anticipated in draft form soon.

AdvaMedDx principles on a flexible, risk-based approach to regulation of diagnostics recommend that, consistent with global risk assessment, risk criteria (apart from risk mitigations) include:

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

Higher risk tests generally comprise tests where a false result could lead to incorrect and harmful clinical management, an unnecessary invasive procedure, or failure to follow up a serious condition. Examples include most companion diagnostics, tests for cancer diagnosis, tests that directly or very strongly influence management of serious disease, and tests for serious or fatal communicable diseases. The underlying factor for determining higher risk tests is the nature of the claims made for them (i.e., intended use).

These tests are distinguished from tests where there are multiple findings used to direct clinical management and where each finding has a specific weight in disease management. They are also distinguished from most tests used to monitor already-detected and -diagnosed disease and genetic tests where the phenotype is already known and is now being confirmed genetically. These tests are also distinct from low risk, well established tests such as cholesterol, iron, and nicotine as well as urine and blood collection kits.

Notification

As a critical step to ensure transparency for FDA and the public on the availability and use of LDTs, all LDT developers must either provide a simple notification of their tests to FDA or comply with facility listing and registration requirements. Facility listing and registration will be mandatory for LDT developers who do not opt to notify FDA. LDT developers also must comply with facility listing and registration requirements once they provide a premarket submission to FDA for review of an LDT.

Adverse Event Reporting

FDA's LDTs framework would require all LDT developers to comply with medical device adverse event reporting requirements. Adverse event reporting represents a critical component of FDA's information-gathering process after it has approved or cleared a medical device for marketing. Adverse event reporting enables corrective action on problem devices and to prevent injury and death by alerting the public when potentially hazardous devices are discovered. Analyzing adverse event reporting also enables detection of unanticipated events and user errors, monitoring and classifying of recalls, updating medical device labels, and developing educational outreach. Using adverse event report data, FDA can detect problems previously unknown as well as problems with similar devices or device categories.

Manufacturers are required to report to the FDA, within 30 days, when they learn that any of their devices may have caused or contributed to a death or serious injury. Manufacturers must also report to the FDA when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Continued Enforcement Discretion

Several categories of LDTs will be exempt from pre-market review, including low risk tests, rare disease testing, traditional LDTs, and unmet needs LDTs. These definitions and scope of categories are explicitly outlined by FDA. AdvaMedDx supports FDA's intent in continuing to exercise enforcement discretion in specific circumstances in which LDTs play a meaningful and needed role in patient care and risks to patients are minimized or appropriately balanced against patient needs even in the absence of FDA pre-market review.

Stakeholder Support

For years, stakeholders have recognized the inadequacy of current oversight of LDTs and called for FDA to enforce existing regulations that apply equally to LDTs as they do to all diagnostics. In 2008, the Secretary's Advisory Committee on Genetics, Health, and Society, in its report entitled "U.S. System of Oversight of Genetic Testing," recommended that "FDA should address all laboratory tests in a manner that takes advantage of its current experience in evaluating laboratory tests."

Writing to the White House in 2012, 24 patient advocacy organizations called for FDA to publish draft guidance on LDT regulation. As one letter from numerous organizations stated, "The promise that advanced diagnostics hold for patients is tremendous, but, at the same time, the increasingly pivotal role of these diagnostics in patient care makes it imperative that their safety and effectiveness is assured by the FDA prior to use."

A document is attached to this testimony that notes comments from a variety of stakeholders that support FDA action on LDTs.

Conclusion

The current diagnostics oversight paradigm results in a tremendous public health gap and highly disparate treatment of tests that are the same from the perspective of patient risk and safety, simply on the basis of whether they are developed by a manufacturer or a laboratory. This is bad public policy, provides an opportunity to use tests in clinical settings that have insufficient clinical data, and stifles investment in high quality products that are assured safe and effective for patients.

AdvaMedDx commends FDA for moving forward to address the patient safety gaps that currently exist in LDT oversight and supports the key elements of the oversight framework that FDA recently announced. We appreciate the opportunity to submit this testimony at today's hearing and look forward to commenting in detail on FDA's draft LDT guidance after it is published.



AdvaMedDx
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Statements on the Regulation of Laboratory Developed Tests

Current Regulatory Gaps and Perspectives on Oversight of LDTs

American Cancer Society Cancer Action Network says...

"Molecular tests, in particular, have become an increasingly integral part of critical treatment decisions about whether or not a particular patient would benefit from a course of therapy. As patients and doctors become more reliant on diagnostic tests to provide this information, it is critical that they are valid and accurate. However, many tests come to market without independent verification of their clinical validity by a government or independent agency. Testing kits should be cleared or approved by the FDA prior to marketing; however, the vast majority of laboratory-developed tests (LDTs) are marketed without such reviews. When the FDA began regulating medical devices, LDTs were relatively simple, low-risk tests. Now, LDTs encompass even the most advanced molecular diagnostics, such as higher risk tests that are essential for safe and effective use of cancer therapeutics or are critical determinants in the treatment of serious, life threatening diseases. With diagnostic testing and targeted therapies on the rise, the stakes are now much higher for cancer patients. LDTs are becoming more numerous, more complex, and have the potential to have a significant impact on health care decisions, and the FDA should provide oversight of LDTs that could pose risk to patients if not fully understood. This should allow the medical community to take full advantage of these new tests."

Letter to U.S. House of Representatives Energy and Commerce Committee,
Comments on 21st Century Cures Initiative
June 13, 2014

Cancer Leadership Council says...

"Over the years the number, complexity, and impact on health care decisions of LDTs have increased, and the differences between FDA-reviewed tests and LDTs have become less clear. In addition, cancer patients have in recent years suffered harm from LDTs that did not provide the accurate and meaningful information that was promised... The draft guidance on [FDA standards for evaluation of LDTs] should be published for public comment and advice without further delay."

Letter to the Obama Administration
November 21, 2012

Patient Advocates say...

"The widespread development and use of a new generation of advanced molecular diagnostics by clinical laboratories without FDA oversight has exposed a significant gap in the regulatory system. We believe the time has come for the Administration to address this regulatory gap and resolve the uncertainty hanging over this critical area of medicine by affirming FDA's oversight of diagnostics."

Letter to the Obama Administration
November 14, 2012

American Heart Association says...

"Because of the moderate-to-high complexity of many newer tests and their interpretation, testing requires the regulatory oversight by an authority capable of fully evaluating both the analytic validity and, especially, the clinical validity. As observed by the American Heart Association, the FDA is ideally suited to perform this function, because it has the clear statutory authority, scientific expertise, and experience in regulating genetic tests. It would be essential that the agency be appropriately resourced to ensure efficient test review and continued access to tests with established clinical validity."

Genetics and Cardiovascular Disease, A Policy Statement From the American Heart Association
July 3, 2012

Ovarian Cancer National Alliance says...

"The difference between a CLIA regulated test and an FDA regulated test is akin to restaurant reviews — CLIA is like a health inspection telling you that the restaurant is clean where FDA is like Zagat telling you the food is good."

"A lower risk test, such as one for predicting baldness, might be regulated by FDA, but a high risk LDT, such as an ovarian cancer diagnostic test, might not be. Clearly, the likely medical interventions doctors would make, and the impact on patients would be very different for these two tests."

The Teal Journal: "Laboratory Developed Tests: What Goes Wrong"
September 2010

National Health Council says...

"The National Health Council (NHC) supports the FDA's decision to reconsider its policy of enforcement discretion over LDTs. Diagnostic tests play a critical role in informing treatment planning for people with chronic disease. The NHC seeks to ensure that all diagnostic tests, including LDTs, undergo an appropriate level of scientific and regulatory oversight."

August 15, 2010+

National Coalition for Cancer Survivorship says...

"The National Coalition for Cancer Survivorship (NCCS) strongly supports the recent initiative by the Food and Drug Administration (FDA) to assert regulatory authority over laboratory-developed tests (LDTs). Our interest in this issue stems from concerns about the lack of reliable oversight of LDTs, which are increasingly important in identifying genetic or other anomalies that are the targets of new pharmaceutical or immunological interventions."

August 11, 2010+

Director of NIH and FDA Commissioner say...

"[P]utting in place an appropriate risk-based regulatory framework is now critical to ensure the validation and quality of tests (called laboratory-developed tests, or LDTs) developed in-house by clinical laboratories."

New England Journal of Medicine Perspective First FDA Authorization for Next-Generation Sequencer
by National Institutes of Health Director Francis Collins, MD, PhD,
and Food and Drug Administration Commissioner Margaret Hamburg, MD
December 19, 2013

Food and Drug Administration says...

"The increasing reliance on diagnostic tests in clinical decision making, combined with the dramatic shift in the number and complexity of LDTs being offered, are posing increasing risks to patients. FDA has been made aware of a number of examples where clinical decisions made on the basis of faulty tests resulted in harm to patients. As a result, FDA has been developing a risk-based framework for regulatory oversight of LDTs that would assure that tests, regardless of the manufacturer, have the proper levels of control to provide a reasonable assurance of safety and effectiveness, while also fostering innovation and progress in personalized medicine."

FDA Report: Paving the Way for Personalized Medicine FDA
October 2013

American Association of Clinical Chemistry says...

"AACC supports the FDA's idea of employing a risk-based classification approach for determining the level of oversight for LDTs."

"Once risk stratification occurs, AACC recommends that high risk LDTs be subject to FDA oversight."

July 19, 2010+

Centers for Medicare and Medicaid Services says...

"CLIA and its implementing regulations do not affect FDA's authority under the FDCA to regulate LDTs or other devices used by laboratories."

"CMS' CLIA program does not address the clinical validity of any test — that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. On the other hand, FDA evaluates the clinical validity of a test under its premarket clearance and approval processes and as a result, has expertise in this area. In other words, the FDCA encompasses clinical validity whereas CLIA does not."

CMS CLIA Overview and LDT Frequently Asked Questions
October 22, 2013

Members of Congress say...

"We have reached a critical point in the development of advanced diagnostics at which it has become essential that FDA move this guidance forward to ensure appropriate and efficient oversight of safe and effective diagnostics."

"The field of diagnostics has changed fundamentally and rapidly in recent years. A new generation of advanced molecular diagnostics — widely developed as LDTs — is increasingly determinative of critical treatment decisions for patients with life-threatening conditions. These advanced diagnostics, the cornerstone of personalized medicine, provide unprecedented insights into the presence and course of diseases and other health conditions."

Joint Letter from Members of Congress to the Office of Management and Budget
August 9, 2013

FDA Commissioner says...

"LDT's have become more sophisticated and complex. Results from these tests are rapidly becoming a staple of medical decision-making, particularly for cancer. But relying on advanced diagnostics to make critical, life-altering treatment decisions exposes patients to obvious risks if these tests do not perform as expected. False results put patients at risk of a missed diagnosis or a wrong diagnosis that could result in either inappropriate treat or no treatment at all. The Agency is working to make sure that the accuracy and clinical validity of high-risk tests are established before they come to market."

FDA Commissioner Margaret A. Hamburg, M.D.
Address at the American Society of Clinical Oncology Annual Meeting, Chicago
June 2, 2013

The New York Times says...

"If a diagnostic test is made by a traditional device manufacturer, the Food and Drug Administration reviews its safety and effectiveness before approving it for marketing. However, if a test is developed by a clinical laboratory for use at its own facilities, it can be sold without a premarket review."

"That bifurcated approach made sense in years past when a medical center might develop a diagnostic test for its own doctors and patients. But the landscape has changed with the advent of more sophisticated tests and the rapid expansion of commercial laboratory companies. Experts are unsure about how well these so-called laboratory-developed tests, or L.D.T.'s, perform in identifying diseases."

"Regulations are long overdue; the draft guidelines should be quickly released for public comment."

New York Times Editorial: The Gap in Medical Testing
July 7, 2013

National Human Genome Research Institute says...

"As the science of genomics advances, genetic testing is becoming more commonplace in the clinic. Yet most genetic tests are not regulated, meaning that they go to market without any independent analysis to verify the claims of the seller. The Food and Drug Administration (FDA) has the authority to regulate genetic tests, but it has to date only regulated the relatively small number of genetic tests sold to laboratories as kits. Whereas the Centers for Medicare and Medicaid Services (CMS) does regulate clinical laboratories, it does not examine whether the tests performed are clinically meaningful. Since the 1990s, expert panels and members of Congress have expressed concern about this regulatory gap and the need for FDA to address it."

National Human Genome Research Institute

United Healthcare says...

"Patients and their physicians need to be able to be confident that diagnostic tests are accurate and are both analytically and clinically valid. The current regulatory infrastructure for genetic tests and molecular diagnostics — which is primarily housed at the FDA and CMS — has important gaps. Current approaches focus on the quality of the testing process at laboratories, rather than evaluating the attributes of an individual test, leaving questions about test quality. Approaches also focus on the safety and efficacy of a subset of tests developed by manufacturers; however, there is minimal oversight of tests developed by laboratories (LDTs), leading to questions of the clinical validity of some tests. Furthermore, there are over 1,000 genetic disorders where tests are developed in labs and are not subject to FDA safety and effectiveness review."

"Personalized Medicine: Trends and Prospects for the
New Science of Genetic Testing and Molecular Diagnostics," March 2012

College of American Pathologists says...

"CAP believes that the FDA should implement a risk-based framework that leverages the resources of other expert bodies and enables FDA to focus on clinical claims made for high-risk LDTs."

August 15, 2010+

The Institute of Medicine's Evolution of Translational Omics Report says...

"Lack of FDA oversight places an often unrecognized demand on academic institutions to provide proper oversight for omics-based test development, validation, and clinical use."

Evolution of Translational Omics — Report Brief

Director of FDA's Center for Devices and Radiological Health Director says...

"FDA has observed the following problems with some LDTs in recent years:

- Faulty data analysis
- Exaggerated clinical claims
- Fraudulent data
- Lack of traceability/change control
- Poor clinical study design
- Unacceptable clinical performance"

Jeffrey Shuren, M.D., Director, Center for Devices and Radiological Health, Food and Drug Administration
Testimony to the House Energy and Commerce Committee Subcommittee on Oversight
and Investigation Direct-to-Consumer Genetic Testing and the Consequences to the Public
July 22, 2010

The Secretary's Advisory Committee on Genetics, Health, and Society Report on U.S. System of Oversight of Genetic Testing says...

"The Food and Drug Administration (FDA) should address all laboratory tests, regardless of how they are produced (i.e., as a commercial test kit or laboratory-developed test)."

"The Committee is concerned by the gap in oversight related to clinical validity and believes that it is imperative to close this gap as expeditiously as possible."

"U.S. System of Oversight of Genetic Testing," April 2008

+2010 references are to comments made in connection with the U.S. Food and Drug Administration's July 19–20, 2010 public meeting, and the associated docket for public comments, regarding Oversight of Laboratory Developed Tests. Docket Number FDA-2010-N-0274.

Mr. PITTS. The Chair thanks the gentleman.
I now recognize Dr. Behrens Wilsey 5 minutes for an opening statement.

STATEMENT OF KATHLEEN BEHRENS WILSEY, Ph.D.

Ms. BEHRENS WILSEY. Good morning, Chairman Pitts, Ranking Member Pallone, and Members of the subcommittee. I am Dr. Kathy Behrens Wilsey, Co-Founder of the Coalition for 21st Century Medicine. On behalf of the Coalition, thank you for convening today's important hearing to address this critical issue in health care innovation, and for inviting the Coalition to testify.

Today, we live in a world in which a woman with breast cancer can confidently and reliably reject toxic and potentially life-threatening chemotherapy because testing has confirmed she will not benefit from such treatment. Without such testing, she would only experience harmful side-effects from a treatment protocol that has been, until very recently, both standard and routine care. With diagnostic test information, she has more certainty that conventional treatment would neither improve the quality of, nor prolong her life. This woman benefits from significant progress in new advanced diagnostics. Most importantly, this progress has substantially improved patient outcomes without diminishing safety, though occurring in the midst of formidable regulatory uncertainty.

I am here today because, despite some well-known examples like the women who now have far greater certainty about their treatment pathway, investment in advanced diagnostics suffers from great uncertainty; uncertainty about evidence development and reimbursement. The overall return is lower for diagnostics than for pharmaceuticals, so while the challenges may appear to be the same, this lower return has resulted in attracting fewer investors and less capital.

Investment in and development of advanced diagnostics has declined in recent years as a direct result of 8 years of regulatory uncertainty. The lack of a clear path for innovation in vitro diagnostics under the current FDA regulations has been evident as FDA proposes and withdraws different proposals, each time rolling back its historic flexible regulatory approach. Prolonging the current regulatory limbo, or worse, implementing an incomplete or overly burdensome regulatory framework, will accelerate the shift to venture capital investment out of advanced diagnostics and into more predictable endeavors.

And so we find ourselves at a crossroads. The overwhelming success of the human genome project and its medical and scientific advances are closer than ever to accelerating what this committee calls 21st Century Cures: early, rapid and comprehensive diagnosis, followed by individualized targeted treatments against serious and life-threatening diseases, and yet the proposed regulation of laboratory-developed tests control progress and fight against cancer, cardiovascular disease, deadly infectious diseases, and countless rare diseases and disorders that can be more effectively and efficiently combated through advanced diagnostics.

The framework put forth by the FDA is no doubt an improvement over the initial draft guidance published in 2006. Yet, in the interest of extending our impressive progress in the development of

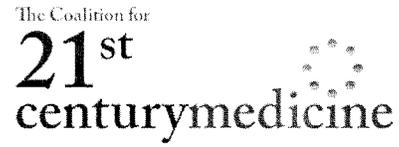
new advanced diagnostics to help patients, and at the same time avoiding additional barriers to innovation, the Coalition recommends the FDA provide detailed substantive guidance on many outstanding issues before its proposed framework is finalized—a framework that starts a clock for compliance among affected laboratories. Specifically, the FDA must, among other things, identify the device within the LDT service, harmonize FDA and CLIA quality systems regulations, which have different and, in certain areas, incompatible purposes, provide clear guidance on requirements for obtaining labeling that is useful for clinicians and patients, and accommodate medical communications between laboratories and treating physicians under an FDA regulatory framework that imposes substantial limitations on proactive communications by medical product manufacturers. We also need a flexible regulatory system which enables the rapid translation of scientific and clinical evidence that so powerfully enables timely access to the newest generation of tests. Additionally, clear and meaningful labeling is critical for physicians and patients, otherwise public and private payers resist providing coverage and patients do not get tested. It literally takes years for payers to approve coverage and payment for advanced diagnostics, and they are not likely to pay if the FDA-approved label suggests that the test cannot be used in a clinically meaningful way. Given the FDA's recent framework, we caution the subcommittee about the potential number of tests that might be subject to premarket review.

Finally, we have concerns that the FDA underestimates the challenges associated with translating regulatory processes developed to oversee diagnostic products that are designed for both broad distribution and use, in contrast to services performed by individual labs. Most venture capitalists appreciate that there are significant differences between the two that could substantially risk the successful implementation of the FDA's plans.

We applaud the subcommittee for exercising its oversight function by holding this hearing, and encourage Congress to continue to work with the FDA throughout the public comment process. We also encourage the subcommittee to consider legislation where necessary, to fill gaps in the regulatory framework, and address potential inconsistencies and duplication across regulatory authorities to ensure that the balance between advancing the public health and facilitated American innovation is maintained.

Thank you.

[The prepared statement of Ms. Behrens Wilsey follows:]



Testimony of

M. Kathleen Behrens Wilsey, Ph.D.
Co-Founder, The Coalition for 21st Century Medicine

Before the
U.S. House of Representatives
Committee on Energy and Commerce
Subcommittee on Health

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

September 9, 2014

STATEMENT SUMMARY

Presented by Dr. Kathy Behrens Wilsey, co-founder of the Coalition for 21st Century Medicine and a life science venture capitalist, investor, board member and executive. Dr. Wilsey served on the President's Council of Advisors on Science and Technology (PCAST) as chairwoman of its Subcommittee on Personalized Medicine. A former director of the National Research Council's Board on Science, Technology and Economic Policy, Dr. Wilsey is a past director, president, and chairwoman of the National Venture Capital Association.

- The United States is at crossroads in the ongoing revolution of personalized medicine, and could fulfill the promise of “21st Century Cures”—early, rapid and comprehensive diagnosis, and individualized, targeted treatments against serious and life-threatening diseases—only if regulators and public and private insurers align toward the objective.
- The proposed regulation of laboratory developed tests, or LDTs, could either facilitate or choke off the current development of similar progress against various cancers, cardiovascular disease, deadly infectious diseases, and countless rare diseases and disorders.
- The Coalition is deeply concerned about how the uncertain regulatory environment has discouraged investment funding in, and development of advanced diagnostics. The lack of a clear path for innovative *in vitro* diagnostics under the current FDA regulations has been evident as FDA proposes and withdraws different proposals to roll back its historic, flexible approach to these innovative tests. We believe that prolonging the current regulatory limbo or, worse, implementing an incomplete or overly burdensome regulatory framework would result in the accelerating loss of investment in American companies and the movement of our innovative discoveries offshore.
- Continued innovation is only possible if the FDA provides clear and reasonable standards that permit physicians and patients to rely upon advanced diagnostics to better guide treatment, and does so before the deadlines and threatened risks of enforcement action under its proposed “framework” guidance take effect.
- FDA must provide detailed substantive guidance on many outstanding issues before its proposed “framework” is finalized, which starts a clock for compliance among affected laboratories: (1) identifying the “device” within the LDT service; (2) harmonizing FDA and CLIA quality systems regulations, which have different purposes; (3) providing clear guidance on requirements for obtaining labeling that is useful for clinicians and patients; and (4) accommodating medical communications between providers—laboratories and treating physicians—under an FDA regulatory framework that imposes substantial limitations on pro-active communications by medical product manufacturers.
- The framework put forth by the FDA is no doubt an improvement over the initial draft guidance published in 2006, but it still leaves far too many critical questions unanswered, and hoping that the agency appropriately resolves those questions in a final guidance presents too great a risk of stifling innovation at a crucial moment in the historic evolution of advanced diagnostics.
- We also encourage the Subcommittee to consider legislation, where necessary, to fill gaps in the regulatory framework and address potential inconsistencies and duplication across regulating authorities to ensure that the balance between advancing the public health and facilitating American innovation is maintained.

Good morning, Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee. I am Dr. Kathy Behrens Wilsey, co-founder of the Coalition for 21st Century Medicine. On behalf of the Coalition, thank you for convening today's hearing to address this critical issue in health care innovation.

The Coalition for 21st Century Medicine represents world renowned diagnostic technology companies, clinical laboratories, researchers, venture capitalists, and patient advocacy groups who are working to develop and promote high quality, innovative diagnostic tests. Founded in 2006, the Coalition has a successful history of working with lawmakers and policymakers to identify meaningful ways to balance regulation and innovation, and to ensure that regulatory policy promotes rapid access to new diagnostic information.

Development of and access to innovative molecular diagnostics is essential to enabling individualized treatment, and has the potential to revolutionize our health care system. However, the potential for advanced diagnostics to help patients has yet to be fully realized due in large part to the widespread perception by many companies and investors that the costs, risks, and barriers associated with diagnostic development outweigh the anticipated returns. This perception has been fueled by a variety of failed attempts to apply a regulatory framework that was not designed, nor is well suited for rapidly advancing *in vitro* diagnostics.

Advances in technology and genomic information are rapidly changing the commercial diagnostic landscape and opening up new opportunities for advanced diagnostic tests. There is perhaps no field in which government policies will play a greater role than in diagnostic

innovation, and have the potential either to slow such innovation or to help lower diagnostic development risks/barriers.

Today's hearing is exceptionally well-timed. It is no exaggeration to say that our country is at a cross-roads in the ongoing revolution of personalized medicine. Because of the success of the Human Genome Project (HGP) and related technologies, we are closer than ever to fulfilling the promise of what this Subcommittee calls "21st Century Cures"-- early, rapid and comprehensive diagnosis, followed by individualized, targeted treatments against the most serious and life-threatening diseases. We have the tests and technology to guide treatments to the right patients at the right time. We can make extraordinary advances in medical treatment, but only if government programs align toward this future.

For the past thirty years, I have been a venture capitalist, investor, board member and executive focused on the life sciences industry. I served on the President's Council of Advisors on Science and Technology (PCAST) from 2001 to early 2009, and was chairwoman of PCAST's Subcommittee on Personalized Medicine. I am a former director of the National Research Council's Board on Science, Technology and Economic Policy, and I was the director, president, and chair of the National Venture Capital Association.

In these and other roles, I have observed first-hand how investment in personalized medicine has produced tests that help inform medical decision making to provide more effective, safer, and more efficient care. However, I also have observed how antiquated government programs designed for a different era – whether they be regulatory oversight or payment – have not been

aligned to promote that progress and in many cases, impede such progress. It is with this in mind that I believe that the proposed regulation of laboratory developed tests, or LDTs, that is set forth in the FDA's Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories "Framework for Regulatory Oversight of Laboratory Developed Tests (LDT)" (the "Draft Guidance") could either facilitate or choke-off the development of diagnostic tests for various types of cancer, cardiovascular disease, deadly infectious diseases, and countless rare diseases and disorders.

We have a keen interest in the extent to which the Food and Drug Administration (FDA) intends to regulate LDTs as medical devices. Since its inception, the Coalition has been working with FDA on developing a reasonable regulatory framework that would apply to all diagnostic testing—both *in vitro* diagnostic test kits as well as LDTs—and we remain committed to that effort. We acknowledge and appreciate the time the FDA has taken to meet and to engage with us over the years, and particularly since releasing this latest guidance, aiming to develop an appropriate regulatory model for advanced diagnostic tests that protects public health and promotes innovation.

Appropriate regulation of *in vitro* diagnostic testing is essential to assuring reliability and accuracy, and fostering public confidence. At the same time, continued innovation is only possible if the FDA provides clear and reasonable standards for test developers that permit physicians and patients to rely upon advanced diagnostics to better guide treatment, and only if the Agency implements such standards before the deadlines and threatened risks of enforcement action under its proposed 'framework' guidance take effect. The Coalition is deeply concerned

that investment in, and development of, advanced diagnostics have already declined as a result of the current, sustained period of regulatory uncertainty. The lack of a clear path for innovative *in vitro* diagnostics under the current FDA regulations has been evident as FDA proposes and withdraws different proposals to roll back its historic, flexible approach to these innovative tests. We believe that prolonging the current regulatory limbo or implementing an incomplete or overly burdensome regulatory framework would result in the accelerating loss of investment in American companies and the movement of our innovative discoveries offshore.

Eight years ago, I helped found this Coalition when the FDA proposed troubling draft guidance to newly regulate a group of novel LDTs under a previously unknown term “*in vitro* diagnostic multivariate index assay” (IVDMIA) tests. For years, the Agency had recognized that “the use of in-house-developed tests has contributed to enhanced standards of medical care ... and that significant regulatory changes in this area could have negative effects on the public health.”¹¹ But when the Agency proposed to reverse this position, stakeholders from across the spectrum of medicine and health care converged to defend the proposition that high quality, innovative diagnostic tests were essential to improving health care and that the draft FDA enforcement policy over so-called IVDMIA was likely to be more harmful than helpful to patients. Since then, we have worked with the FDA, Congress and the Administration to find the balance between regulation and innovation that bolsters public confidence while promoting rapid access to accurate and reliable new diagnostic information. Despite best efforts on the part of many, today, we are still too far away from finding that balance. The framework put forth by the FDA is no doubt an improvement over the initial draft guidance published in 2006, but it still leaves far too many critical questions unanswered, and hoping that the agency appropriately resolves

those questions in a final guidance presents too great a risk of stifling innovation at a crucial moment in the historic evolution of advanced diagnostics.

We consequently applaud the Subcommittee for exercising its oversight function by holding this hearing, and encourage Congress to continue to work with the FDA throughout the public comment process. We also encourage the Subcommittee to consider legislation, where necessary, to fill gaps in the regulatory framework and address potential inconsistencies and duplication across regulating authorities to ensure that the balance between advancing the public health and facilitating American innovation is maintained.

There is no question that we have already made enormous progress since 1987 when the Human Genome Project was initiated under President Reagan in the face of widespread skepticism against this unprecedented, multidisciplinary enterprise. But with the sustained vision and material support of this Committee, of Congress, and of successive Administrations, the scientific community and American companies struggled, collaborated, and succeeded—beginning what National Institutes of Health (NIH) Director and pioneering scientist Francis Collins describes as “the dawning of the genomic age.”

Since the human genome was unlocked, there has been an explosion of research and innovation dedicated to diagnosing and treating human disease better, sooner, and faster. According to the NIH, there are tests available for about 2,500 diseases, with many more in development.ⁱⁱ Today, the United States leads the world in translating “bench” science into new diagnostics and in forming early-stage companies that will develop paradigm-changing services and products. We

have already made great strides in understanding which patients will or will not benefit from specific drugs, and have seen some early achievements in tailoring drug treatment for individual patients.

Notwithstanding this progress, the Coalition believes that delivering further on the hopes for, and promise of personalized medicine hinges on settling two strategic issues that face this Congress and the communities of scientists, innovators, regulators, and patients you have convened today:

- For years, advanced diagnostics have been under a cloud of regulatory uncertainty created by changing federal proposals to regulate LDTs, and by doubts cast on the integrity and adequacy of existing federal standards under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. Flexible standards must be established that allow reliable and accurate advanced diagnostics to guide treatment by informed physicians. The Coalition believes that the FDA can work in concert with Congress and stakeholders to create an appropriate and flexible system of regulation for all *in vitro* diagnostic testing.
- If a rigid regulatory system is established that does not provide for timely access to accurate and reliable tests with clear and meaningful labeling for physicians and their patients, public and private payers will resist the coverage of, and payment for, advanced diagnostics. Without meaningful labeling or insurance coverage for these tests, physicians in turn will remain reluctant to order tests that may be helpful in the management of their patients. Today, it literally takes years for payers to approve

coverage and payment for advanced diagnostics. If these tests are available only with labeling claims that do not support the use of the tests to assist patient management decisions and under a regulatory framework which severely hampers clinical laboratory service providers from interacting with treating physicians so they have a better understanding how to use their tests in patient management, the adoption and use of personalized medicine will be stymied. We will not see the improved patient outcomes and reduction in unnecessary treatment that otherwise are already being achieved.

We are committed to working with FDA to strike the right balance between assuring public health and facilitating innovation in promulgating flexible regulations for all diagnostic tests—LDTs and IVDs. However, the Coalition is concerned that the proposed framework is incomplete, creates substantial uncertainty, and does not reflect a careful and important balance that recognizes the value and benefits that advanced diagnostics offer to patients, providers, and payers. The Coalition believes strongly that any future regulatory framework must be premised on the understanding that clinical labs today are offering new and important tests to informed physicians who are sufficiently knowledgeable about their technology and their potential clinical utility to seek them out for their patients. Developing a balanced risk-based system of regulation is only possible if the benefits and value of reliable and accurate advanced diagnostics in guiding treatment is fully understood by the Agency.

In the spirit of striking this balance, the FDA should thoughtfully articulate the public health risk supporting this guidance, so that this risk can be more carefully balanced against the proposed regulatory framework. The framework and the specific proposal to mandate adverse event

reporting, for example, presupposes—without meaningful data or other analytical bases—that there are substantial safety risks affecting American patients from the use of LDTs. A reliable presentation and understanding of the potential risks is a key component of evaluating any regulatory action.

Additionally, the Coalition is greatly concerned that the FDA substantially underestimates the number of LDTs subject to its proposed premarket review requirements. Today, thousands of clinical laboratories perform LDTs to give providers access to data that enable the development of individualized, patient-specific plans of care. For example, certain LDTs are capable of identifying patients susceptible to disease(s) and/or patients that may respond (or not respond) to a particular treatment. According to the Centers for Medicare and Medicaid Services (CMS), there are over 11,000 CLIA-certified laboratories qualified to perform “high-complexity” testing, including LDTs. We estimate that many molecular markers are offered as LDTs by hundreds, if not thousands of laboratories across the country. This would translate into potentially tens of thousands of premarket submissions to the FDA. We believe that the proposed framework creates a meaningful possibility, even with a protracted timeframe for implementation, that the Agency could burden its limited staff with a growing backlog of premarket submissions, inhibit insurance coverage and payment, and restrict patient access to innovative tests.

We also have concerns that the FDA underestimates the challenges associated with translating regulatory processes developed to oversee diagnostic *products* that are designed for broad distribution and use in contrast to *services* performed by individual laboratories. Most venture

capitalists appreciate that there are significant differences between the two that could substantially risk the successful implementation of the FDA's plans

We continue to believe that appropriate regulation is possible that balances the need to ensure patient safety with the need for diagnostic testing to help physicians and patients make informed and timely decisions about patient care. Without this balance, continued development and investment in better, more useful, and even safer diagnostic testing will be in jeopardy—and the patients and providers who would benefit from such tests will experience significant, unnecessary delays in access to critical diagnostic information and appropriate life-saving therapy.

Most importantly, because the proposed framework focuses on procedural milestones, it leaves unclear many of the critical issues and questions that must be addressed well before any of its proposed deadlines take effect. Absent resolution of these questions before guidance is published in final form, clinical laboratories would be simply unable to comply with the new requirements when the framework guidance is finalized. While we understand that FDA intends to address the unanswered issues and inconsistencies in the proposed framework, and will receive extensive public comments, it is critical that the Agency answer these questions before publishing a final guidance. The critical balance that must be struck will be elusive if FDA publishes a final guidance establishing new regulatory requirements that do not satisfactorily and completely resolve these fundamental questions.

To that end, the Coalition strongly encourages the FDA to publish additional draft guidance for comment as well as FAQ documents similar to those issued by CMS so that stakeholders will be able to understand, anticipate and comply with the new regulatory requirements well in advance of any final guidance.

The substantive issues raised by the proposed framework, which must be answered before FDA proceeds further, range from fundamental concerns to technical questions. Following are just some of the significant and critical issues that urgently require answers:

Device or Laboratory Practice?

- How would FDA distinguish a regulable “medical device” from laboratory services in an LDT? The former are analogous to test “kits” currently manufactured then distributed to laboratories to perform, while the latter are the practice of laboratory medicine outside of the Agency’s statutory authority.

Labeling.

- How will FDA ensure that labeling is meaningful for physicians and reimbursable by third party payors for patients—an issue that applies to all *in vitro* diagnostic testing (IVDs, as well as LDTs)?
- How would FDA labeling requirements apply in the absence of a distributed or tangible “box” on which to put a label, or a person or entity to “receive” the “box” or the “labeling”?

Manufacturing and Harmonization with CLIA.

- Medical device Quality Systems Regulation (QSR) requirements would apply upon filing of a premarket submission with the Agency, but the Draft Guidance does not adequately tell clinical laboratories how to comply. As one example, what constitutes a malfunction of a finished device if the test is an LDT?
- How does FDA intend to apply its rules on test design and quality systems to laboratories, and how would such requirements be reconciled with laboratories' continuing obligation to comply with CLIA quality systems requirements on those same activities?

Communications with Laboratories and Providers.

- How would FDA manage conflicting requirements governing consultations with physicians about patient test results? Under the practice of laboratory medicine, CLIA requires disclosure of known information relevant to use of a test by certified laboratory to a treating physician—without regard to “labeling claims.” This pro-active approach to dissemination of information by a clinical laboratory may be inconsistent with the restriction on dissemination of information by a medical device manufacturer under FDA regulation.
- What types of diagnostic or patient treatment claims would be permissible, and what kinds of evidence would be required by FDA?

We recognize that the FDA will receive extensive feedback from stakeholders, and the process of finalizing the draft guidance may take many months, if not years, to complete. The Coalition plans to submit public comments as well, but our concern is that reprising the protracted and unsuccessful guidance development that took place over IVDMIAs would prolong the existing regulatory uncertainty for clinical laboratories, providers, and health systems, with adverse implications for LDT coverage and reimbursement, patient access, and investment in personalized medicine. Ultimately, this Subcommittee may be called upon to assess the necessity of expanded FDA regulation and to establish through legislation clear regulatory standards to address what historically has been a grey area of the Agency's legal jurisdiction.

* * * *

Endnotes

¹ Medical Devices: Classification/Reclassification; Restricted Devices: Analyte Specific Reagents. Washington, D.C.: Food and Drug Administration, 1997.

¹¹ Personalized Medicine: Matching Treatments to Your Genes. National Institutes of Health, December 2013.

Mr. PITTS. The Chair thanks the gentlelady.
I now recognize Mr. Mertz 5 minutes for opening statement.

STATEMENT OF ALAN MERTZ

Mr. MERTZ. Thank you, Chairman Pitts and Ranking Member Pallone, for the opportunity to testify today. I am Alan Mertz, President, American Clinical Laboratory Association, ACLA, and we represent the Nation's leading providers of clinical laboratory services.

I also want to begin by applauding Chairman Upton and Representative DeGette for launching the 21st Century Cures Initiative.

Through the innovations in clinical laboratories, we are diagnosing diseases earlier and more precisely for diabetes, cancer, and infectious and rare diseases. With these powerful new diagnostic tools, patients have access to more targeted and effective therapies sooner, which inevitably increases the quality of care, saves lives and lowers cost.

America is the leader in this diagnostic medicine revolution, and recent advancements in genetic and genomic tests have created over 116,000 jobs, and \$16.5 billion in annual economic output. A reasonable and flexible framework is essential to preserving this vital leadership role that we have in the United States.

ACLA is greatly concerned by the FDA's notice of intent to issue guidance that would completely alter how clinical laboratory tests will be made available to patients. We do not believe that the FDA has the statutory authority to regulate laboratory services, and even if they did, we do not believe that it is appropriate to create a whole new regulatory process through guidance documents.

The laboratory industry is already extensively regulated under an interlocking framework of federal laws, state laws, and peer review-deemed authorities. As has been discussed today, the primary federal law governing labs is CLIA, which creates stringent requirements governing the operation of clinical labs and their personnel to ensure the safe and accurate function of labs and testing services they provide. Further, peer review authorities add additional expertise in reviewing both the operation of the lab, and the analytical and clinical validity of the tests. Operating under this comprehensive yet flexible LDT oversight framework, the field of laboratory medicine has produced some of the most spectacular advances in diagnostics.

In short, LDTs have become ubiquitous in clinical patient care. They range from the most common tests that many of us will be familiar with, like pap smears, to the most advanced molecular and genetic tests in cancer and heart disease. Importantly, the vast majority of new genetic and molecular tests are LDTs, and most FDA-approved and cleared kits are based upon tests originally offered as LDTs. Although the FDA claims that it has no interest in duplicating CLIA's oversight requirements, the FDA notification that came out does not address how they avoid such duplication. There has not been any discussion of how any additional regulation by the FDA would interact with the regulation already under CLIA. There are many areas of commonality and overlap, specifically as it pertains to validation, inspections, quality system regulation,

and yet the FDA has not clarified how it propose the two regulatory authorities working in such a way as to not overburden the lab industry, and slow the development of and access to these vital diagnostic tools. Frankly, we are deeply concerned that the documents released failed to take into account the fundamental differences between a device manufacturer and a clinical laboratory. Unlike a device manufacturer, a clinical laboratory is an integrated operation consisting of highly trained and certified personnel who design, validate, perform, and interpret laboratory tests. 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.

Lastly, I need to emphasize the enormous scale of the increase in regulatory oversight. According to FDA's framework, the Agency will not define high risk or identify how many tests will require premarket approval for several years. The potential workload for the FDA is staggering. There are over 11,000 highly complex laboratories that perform laboratory-developed tests, and the total volume of LDTs numbers at least in the tens of thousands, and our own surveys of our members indicate it may be over 100,000 laboratory-developed tests. In comparison, last year the FDA approved only 23 premarket applications for diagnostic tests.

In conclusion, the ACLA shares the goals of everyone here in ensuring patient access to accurate, reliable, and meaningful tests. We have long supported modernizing the regulatory requirements under CLIA to keep pace with changing technology. We are confident that this can be accomplished without duplicative regulation, oversight, and cost, while maintaining our status as a global leader in diagnostic innovation. We look forward to continuing to work with this committee, with Congress, the FDA, CMS, and other stakeholders on policies that encourage innovation, ensure safety, and maintain patient access to these diagnostic services.

And with that, I thank you and look forward to your questions.
[The prepared statement of Mr. Mertz follows:]



Statement
Of
Alan Mertz,
President,
The American Clinical
Laboratory Association
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
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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 *Oncotype 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.

Oncotype 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 exempted. 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/PM-3-Approvals/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.

Mr. PITTS. The Chair thanks the gentleman.

I now recognizes Dr. Newton-Cheh 5 minutes for an opening statement.

STATEMENT CHRISTOPHER NEWTON-CHEH, M.D.

Dr. NEWTON-CHEH. The Chairman Pitts, Ranking Member Pallone, and Members of the subcommittee, thank you for giving me the opportunity to testify before you today. My name is Christopher Newton-Cheh, I am a cardiologist at Massachusetts General Hospital, specializing in heart failure and cardiac transplantation, and an Assistant Professor of Medicine at Harvard Medical School. I am also a cardiovascular geneticist, investigating the root causes of cardiovascular disease, the leading cause of morbidity and mortality worldwide.

Today, I speak to you not only as a clinician and researcher, but also as a volunteer for the American Heart Association, a nonprofit organization dedicated to building healthier lives, free of cardiovascular disease and stroke. I am concerned about the lack of enforcement of regulation on laboratory-developed tests.

The potential for personalized medicine to improve health and improve the practice of medicine is great. Biomedical research continues to build on the sequencing of the human genome to better understand the genetic component of disease, notably in the discovery of new genetic markers associated with disease risk, as well as drug advocacy and toxicity.

As we continue to develop a greater understanding of the genetics of human disease, we will move away from one-size-fits-all medicine, to more targeted and effective prevention, treatments and even cures. However, it is imperative that these tests are scientifically credible.

Over the past few years, a greater number of LDTs have come onto the market without FDA review that purport to inform individuals of their risk for cardiovascular disease, and which medicines and dosages will be most effective or ineffective in treating their disease. Expert consensus guidelines summarize research evidence, but there is no regulatory mechanism enforced that attempts to compare such evidence to claims made in marketing these tests. The current CLIA-approval process ensures only the analytical validity or accurate measurement, but fails to address clinical validity; whether a test result is clinically important to a patient's health decision-making.

In the absence of such an independent examination, health care professionals, patients, and payers have no assurance of the value and limits of each test. The genetics of some relatively rare cardiovascular conditions caused by single mutations, like long QT syndrome and hypertrophic cardiomyopathy, has been well characterized, and LDTs have been critical components of medical care, family screening, and development of therapeutics for such diseases. However, we are in the early stages of understanding how each person's risk for common disease is influenced by their DNA. An individual's risk of heart attack, heart failure, or atrial fibrillation is a complex interaction of their genetics, their behavior, and their environment.

A 2006 investigative study by the GAO observed the genetic testing companies they investigated “mislead consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information to consumers.” And the FTC issued a statement warning the public to be “wary of claims about the benefits these products supposedly offer.” The public is not equipped to do this on its own.

Despite the remarkably rapid progress that has been made in our understanding of the genetics of cardiovascular disease in recent years, it is not yet possible to assess a person’s DNA to evaluate their risk for most common diseases with sufficient accuracy on which to base treatment decisions. It is clear that some genetic tests lack scientific credibility. Allowing these tests to continue to be marketed without rigorous oversight increases the risk of undermining public and health care provider confidence in the utility of employing genetic tools to improve health care. There are differences between a test kit shipped out to laboratories and an LDT that is performed in a single laboratory. However, regardless of how and where the test is performed, the interests of health care providers and patients remain the same. They need to have the same degree of confidence that it is a high quality test, where the claims of its validity are substantiated by science, and its application to improve patient health established.

I have had patients come to me with genetic tests that suggest slightly increased risks of atrial fibrillation or heart attack, but they are confused because their regular physicians do not know how to interpret results. They ask me whether they should take aspirin, cholesterol-lowering statins, or blood thinners. These are medications with risks and benefits that must be carefully matched to individual patient risks. Statins have been well established to lower risk of heart attack, and people with coronary disease are at high risk of it. A currently marketed genetic test purports to determine whether they are likely not to respond to a statin, or to have higher risk of heart attack. The small studies that initially supported this claim have been completely debunked by much larger studies, but the marketing continues. Not taking a statin because a patient or their doctor believes falsely that they will not respond could contribute to a potentially fatal outcome. This cannot continue. The AHA applauds the FDA for its decision to reconsider its enforcement discretion with regard to the regulation of LDTs. This is the right thing to do for patients.

Thank you very much. I will be happy to answer any questions you may have.

[The prepared statement of Dr. Newton-Cheh follows:]



**Testimony of Christopher Newton-Cheh, MD, MPH
Volunteer for the American Heart Association**

**Before the House Energy and Commerce Subcommittee on Health
*21st Century Cures: Examining the Regulation of Laboratory Developed Tests***

**Rayburn House Office Building, Room 2322
September 9, 2014**

Introduction

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee.

Thank you for giving me the opportunity to testify before you today.

My name is Christopher Newton-Cheh. I am a cardiologist at Massachusetts General Hospital, specializing in heart failure and cardiac transplantation, and an Assistant Professor of Medicine at Harvard Medical School.

I am also a cardiovascular geneticist and spend a considerable amount of time in the laboratory investigating the root causes of cardiovascular disease, a leading cause of morbidity and mortality worldwide. My colleagues and I are focused on using clinical research to translate genetic discoveries into an improved understanding of human disease, identification of new therapies, and the ability to predict individual patient's risk of disease, as well as positive and negative responses to drugs. In particular, we are seeking to identify genetic variants that underlie sudden cardiac death and hypertension.

Today, I speak to you not only as a clinician and researcher, but also as a volunteer for the American Heart Association, a non-profit organization dedicated to building healthier lives, free of cardiovascular diseases and stroke. I am concerned about the lack of enforcement of regulation on laboratory-developed tests (LDTs). It is important to note that many of these tests have not been clinically validated and are used by patients and providers to make important treatment decisions that can result in further adverse events if the information is neither accurate nor reliable.

Promise of personalized medicine

The potential for personalized medicine to improve health and improve the practice of medicine is great. Our evolving knowledge of how genes and lifestyle combine to affect our health is transformational. As we continue to develop a greater understanding of the genetics of cardiovascular disease and stroke in particular, we will move away from “one-size-fits-all” medicine to more targeted and effective prevention, treatments, and even cures.

Genetic tools are increasingly being integrated into health care in the United States, including their use in the diagnosis and treatment of cardiovascular disease. Biomedical research, including that funded by the American Heart Association and the National Institutes of Health, continues to build on the sequencing of the human genome to better understand the genetic component of cardiovascular disease, notably in the discovery of new genetic markers associated with disease risk as well as drug efficacy and toxicity. As our knowledge of the genetic underpinnings of cardiovascular disease expands, we anticipate there will be many opportunities to use genetic tests to predict or preempt disease, and to treat it more effectively. However, it is imperative that these tests are scientifically credible.

Modern market of laboratory-developed tests

As a result of our increased understanding of the role genetics plays in disease, many new tests are now on the market and are promoted to predict, prevent, and treat cardiovascular disease more effectively. Many scientists, including myself, have expressed concern that advertised claims may not be supported by science. Nevertheless, these genetic tests remain on the market and are inadequately regulated. A lack of oversight means there is no guarantee of test quality and performance and that doctors – attempting to make an accurate diagnosis or prediction of risk– and patients – interested in reducing their risk for disease – may receive and take action based on an inaccurate or misleading result.

Over the past few years a greater number of laboratory-developed tests have come onto the market—without FDA review—that purport to inform individuals of their risk for cardiovascular disease, the likelihood that they will develop risk factors for cardiovascular disease, and which medicines and dosages will be most efficacious or ineffective in treating their cardiovascular disease. Unfortunately, these tests typically come to market without any independent verification by a government agency of their clinical validity. Expert consensus guidelines summarize research evidence but there is no regulatory mechanism enforced that attempts to compare such evidence to claims made in marketing such tests. Whereas testing kits are required to be cleared or

approved by the FDA prior to marketing, the vast majority of tests are laboratory-developed tests, marketed without such review. The current CLIA approval process ensures only the analytical validity, or accurate measurement, but fails to address clinical validity, whether a test result is clinically important to a patient's health decision-making. In the absence of such an independent examination, health care professionals, patients and payors have no assurance of the value and limits of each test.

Particularly alarming has been the growth of a market directly selling genetic tests of unknown clinical validity, rather than patients being offered genetic testing services from qualified health care professionals. Such tests purport to analyze a customer's DNA to establish their risk for myocardial infarction, hypertension, atrial fibrillation, as well as a host of other diseases.

I am greatly concerned that the test claims made by companies marketing them may not reflect current science. The genetics of some relatively rare cardiovascular conditions caused by single mutations - like Marfan syndrome, Long QT Syndrome and hypertrophic cardiomyopathy - has been well characterized, and LDTs have been critical components of medical care, family screening and development of therapeutics for such diseases. However, we are in the early stages of understanding how each person's risk for common heart diseases and stroke is influenced by their DNA. An individual's risk of myocardial infarction, heart failure or atrial fibrillation is a complex interaction of their genetics, their behavior and their environment.

As you know, the American Heart Association is not alone in expressing these concerns. A 2006 investigative study by the U.S. Government Accountability Office (GAO) observed that genetic testing companies they investigated "mislead consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information to consumers". Responding to the GAO report, the Federal Trade Commission issued a statement warning the public to be "...wary of claims about the benefits these products supposedly offer." The public is not equipped to do this on its own.

In 2010 the GAO investigated four companies that market genetic tests directly to consumers and provide direct access to genetic testing services. The GAO again found the companies to be misleading customers, concluding that the test results offered by these companies are of "little or no practical use". With the tests offered by companies investigated in this and the 2006 report, I am especially concerned about the claimed predictive value of tests sold directly to consumers for determining risk of cardiovascular disease. Despite the remarkably rapid progress that has been made in our understanding of the genetics of heart disease and stroke in recent years, it is not yet

possible to assess a person's DNA to evaluate their risk for most common diseases with sufficient accuracy on which to base treatment decisions.

It is clear that some genetic tests lack scientific credibility. Allowing these tests to continue to be marketed without rigorous oversight increases the risk of undermining public and health care provider confidence in the utility of employing genetic tools to improve health care.

Need for oversight of laboratory-developed tests

Ultimately, we may be able to achieve significant medical advances with the development of new genetic tools that assist with preventing and treating heart disease and stroke. But, for this to come to fruition, health care providers need accurate and reliable tests they can interpret to guide shared decision-making with patients. The success of this effort to personalize medicine is also dependent upon acceptance by the American public that undergoing genetic testing will lead to improved health outcomes. The independent review by the FDA of laboratory-developed tests will help establish whether tests are valid, and ensure that information from tests is accurately communicated to physicians and patients.

I recognize that there are differences between a test kit shipped out to laboratories and a laboratory-developed test that is performed in a single laboratory. However, regardless of how and where the test is performed, the interests of health care providers and patients remain the same. They need to have the same degree of confidence that it is a high quality test, where the claims of its validity are substantiated by science, and its application to improve patient health established. Genetic tests therefore need to be independently evaluated by the FDA with the same rigor as tests marketed as kits. Such a level of scrutiny is especially important when tests are being used for guiding critical medical decisions, such as drug selection or dosage.

The oversight of laboratory-developed tests is all the more urgent as new types of testing come onto the market. Whereas genetic testing previously involved looking for a single, well-characterized mutation or chromosomal abnormality known to be associated with a rare disorder, a much wider variety of testing methodologies is now employed. It is now possible to genotyped millions of genetic variants or sequence all 20,000 genes at once, uncovering scores of variants of uncertain clinical relevance. One type of test examines one letter changes in DNA sequence (known as single nucleotide polymorphisms [SNPs]), to obtain a result. Little may be known about the SNPs beyond the observation that their presence or absence correlates with slightly increased or decreased disease risk. Another type of test detects not sequence but gene expression, where levels of activity of a number of genes are tested. In such scenarios, the analysis of the raw data and interpretation is more complex than, for example, the simple

inheritance of a well-characterized point mutation known to cause a disease. The clinical validity of such tests is often not clear to health care providers or patients.

Impact of unregulated laboratory-developed tests on patient care

I have had patients come to me with genetic tests that suggest slightly increased risks of atrial fibrillation or myocardial infarction but they are totally confused because their regular physicians do not know how to interpret results. They ask me whether they should take aspirin, beta blockers, cholesterol-lowering statins or blood thinners. These are medications with risks and benefits that must be carefully matched to individual patient risks. Statins have been well established to lower risk of heart attack in people with coronary artery disease or at high risk of it. A currently marketed genetic test purports to determine whether they are likely not to respond to a statin or to have higher risk of heart attack. The small studies that initially supported this claim have been completely debunked by much larger studies but the marketing continues. Not taking a statin because a patient or their doctor believes falsely that they will not respond could contribute to a potentially fatal outcome. This cannot continue.

FDA's proposed regulatory framework for laboratory-developed tests

The American Heart Association applauds the Food and Drug Administration (FDA) for its decision to reconsider its enforcement discretion with regard to the regulation of laboratory-developed tests—this is an important step in the right direction for patients.

The American Heart Association has long been concerned by the unregulated marketing of genetic laboratory-developed tests. In a 2012 Association policy statement on genetics and cardiovascular disease, the Association notes that "all genetic tests, including laboratory-developed genetic tests, should be required to undergo independent review to confirm their analytic and clinical validity". For some time now, the Association has expressed concern that there are significant gaps in the oversight of genetic testing, and that enhanced oversight is fundamental to ensure that new discoveries are translated into reliable informational tools for healthcare professionals and improved health outcomes for patients.

The Association believes that ultimately it will be in the best interests of patients for laboratory-developed tests to be approved or cleared just as tests marketed as kits are currently regulated. One of the challenges the agency faces in regulating LDTs, of course, is that numerous tests are already on the market, and many are utilized as part of patient care. The Association recognizes that the agency may not currently have all the resources it would need to quickly review all currently marketed tests to determine through an approval or clearance process their safety and effectiveness.

I would urge the FDA to release the draft guidance as soon as the 60-day notice window expires so that all stakeholders have the ability to review and begin a public dialogue about how best to proceed. This is the right thing to do for patients.

Conclusion

Advanced diagnostics hold tremendous promise for patients, but the increasingly pivotal role of these diagnostics in patient care makes it imperative that their safety and effectiveness is assured by the FDA prior to use. The FDA standards are intended to reassure patients and providers on the reliability and usefulness of diagnostic tests and set clear parameters for developers of new tests.

I sincerely thank you for giving me this opportunity to testify before you today. I would be happy to answer any questions you may have.

Mr. PITTS. The Chair thanks the gentleman.
I now recognize Dr. Sawyers 5 minutes for opening statement.

STATEMENT OF CHARLES SAWYERS, M.D.

Dr. SAWYERS. Good morning, Mr. Chairman and distinguished Members of the subcommittee. My name is Dr. Charles Sawyers. I am an oncologist and a cancer researcher, and the chair of a cancer research department at Memorial Sloan Kettering Cancer Center in New York. I am also the immediate Past-President of the American Association for Cancer Research, or AACR, which is the world's oldest and largest cancer research organization, with over 35,000 members, representing basic translational, clinical researchers, health care professionals, patients, and advocates in the U.S. and abroad, and I am honored to appear before you today.

I want to begin by reminding us what a remarkable time it is in cancer research and with the development of many new cancer drugs. This all dovetails from our investment as a country in 1971 to defeat cancer through the National Cancer Act. Now, more than 4 decades later, this commitment is finally paying off. By my last count, over 45 new lifesaving cancer drugs were approved just in the last 10 years, including one just last Friday.

So I want to point out three things that came together to make this slope of increase in cancer drug development happen so quickly over the last 10 years. First, we finally understand the cause of cancer. Cancer is a disease of mutant genes, and by knowing the names of those genes and how they cause cancer, we can discover new drugs that kill cancer cells by attacking them at their roots. The second is the human genome project. By knowing the names of all the genes in our DNA, we have been able to catalog over the last several years all the ones that are mutated in cancer. This knowledge teaches us that cancer is not just 10 or 20 different diseases called lung, colon, breast and prostate cancer, but hundreds of diseases defined by the mutant genes that cause them. This also empowers us to develop the drugs to treat each cancer more effectively. And the third is technology. Just 5 years ago, DNA sequencing was so specialized that it could only be carried out in research settings, using highly curated tumor specimens, but today, this technology is routinely deployed in many of the major cancer centers throughout our country, and tomorrow, this technology will become a routine part of workup of all cancer patients.

I know this from firsthand experience. Fifteen years ago, I co-led the first clinical trial of a drug called Gleevec that is a highly effective drug for a form of blood cancer known as chronic myeloid leukemia, or CML. All patients with CML have a very specific gene mutation, and prior to Gleevec, had a life expectancy of just a few years, but now CML patients live for decades simply by taking this pill once a day that targets the cancer cells without the side-effects of chemotherapy or radiation. In fact, many of the patients I treated on the first clinical trial back in 1999 are alive and well today. And similar stories can be told for melanoma, lung cancer, colon cancer, and sarcoma and so on, and medical historians will look back and call this the golden age of cancer therapy.

So why am I here today to talk about LDTs? Well, it is obvious, because diagnostics are critical to the success of this targeted can-

cer therapy. Indeed, as we have heard from many of the speakers today, the mantra of personalized medicine is the right drug for the right patient. And the FDA recognizes this and approves these new targeted cancer therapies in conjunction with the so-called companion diagnostic which we have heard about, which undergoes a rigorous validation process, just like the drug. Therefore, a safe, reliable, and effective diagnostic test is as important as a safe, reliable, and effective drug.

Now, the problem is urgent because gene sequencing will soon become a routine part of cancer care. Hundreds of thousands, if not millions, of patients are going to be impacted by this technology in the coming years, and I think we all agree that physicians and patients must be able to trust the claims made by the developers of these tests, especially when they are used to determine the treatment regimen for a cancer patient. Too much is at stake to compromise on the regulatory standards that govern them.

And gene sequencing technology is evolving very rapidly, one of the most innovative industries I have seen, and we are just at the tip of the iceberg of what may be possible. I think we will soon be able to detect cancer mutations in a single drop of blood. Many innovative companies are entering the field and are looking for clarity from the FDA on how to commercialize these and related technologies. Just as with drug approvals, a clearly-defined regulatory process will lead to greater innovation and investment.

For all these reasons, ACR, which I represent, as well as my own experience in the cancer research field, I applaud the FDA for proposing a classification of LDTs based on the risks posed by the test to the patient. Having a single strict regulatory approval standard will reassure the American public that the tests used in a high-risk health care setting are safe, accurate, and effective, and will encourage the private sector to invest in this promising area of medicine.

I want to close by submitting for the record the ACR's policy statement on the regulation of diagnostics entitled, reliable and effective diagnostics are keys to accelerating personalized cancer medicine and transforming cancer care.

Thank you.

[The prepared statement of Dr. Sawyers follows:]



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

**Testimony Before
Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives**

Charles L. Sawyers, MD

Immediate Past President of the AACR

Chair, Human Oncology and Pathogenesis Program

Memorial Sloan Kettering Cancer Center

New York, NY

September 9, 2014

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

**Testimony of Charles L. Sawyers, MD, Chair, Human Oncology and Pathogenesis
Program, Memorial Sloan Kettering Cancer Center**

Good morning, Mr. Chairman and distinguished Members of the Subcommittee. I am the immediate past president of the American Association for Cancer Research (AACR), and serve as Chair of the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center. I am honored to appear before you today to provide you with a perspective from the AACR on the recent notification offered by the Food and Drug Administration regarding the regulation of Laboratory Developed Tests (LDTs). Specifically, I will address the ways in which we believe this potential framework for regulatory oversight will protect patients, incentivize innovation, and advance the practice of personalized or precision medicine.

The mission of the AACR is to prevent and cure cancer through research, education, communication, and collaboration. Founded in 1907, the AACR is the world's oldest and largest cancer organization dedicated to accelerating advances in cancer research to benefit patients. The AACR's membership includes more than 35,000 basic, translational, and clinical researchers, health care professionals, patients and patient advocates residing in the U.S. as well as 96 other countries.

Because the AACR encompasses the entire continuum of cancer research and biomedical science – from the laboratory to the clinic including public policy – we are able to marshal the full

spectrum of expertise in the cancer community to accelerate progress in the prevention, detection, diagnosis, and treatment of cancer.

Cancer researchers today are leading the way in the exciting area of personalized or precision medicine, where scientists are increasingly developing treatments that are precisely targeted to the unique molecular and genetic characteristics of an individual's cancer. However, the success of these personalized treatments depends in no small measure on diagnostic tests that are reliable.

The Promise of Personalized or Precision Medicine

The knowledge of cancer's underlying biological causes, enabled through sustained investment by the federal government, primarily through the National Institutes of Health, has catalyzed a shift from the classification of cancer by site of origin, like lung or breast cancer, to classification by molecular subtype. This means that we are rapidly moving away from the era of one-size-fits-all cancer treatments that involve surgery, radiation, and chemotherapy, and are instead utilizing more sophisticated and highly innovative DNA sequencing technologies to provide patients with more opportunities for targeted treatments and personalized or precision medicine. More and more, we are treating cancer patients based on the specific molecular characteristics of his or her tumor(s), which is increasingly determined using highly complex DNA sequencing technologies. The promise of this approach is immense, and we are now ensuring that these advances are being applied to various forms of cancer with increasing speed and success.

I know the impact of molecularly targeted cancer therapy from firsthand experience, having led the first clinical trial of a drug called Gleevec that is highly effective in a form of blood cancer known as chronic myeloid leukemia. Patients with this formerly devastating disease now live for decades simply by taking a pill once a day that precisely targets the cancer cells. In fact, many of the patients I treated on the first clinical trial in 1999 are still alive and well today.

Since the approval of Gleevec in 2001, many additional targeted therapies have been developed and approved for a range of cancers; including previously deadly cancers -45 such personalized or precision medicines have gained FDA approval as of July 31 this year¹. The benefit of targeted cancer therapy is that we are able to hone in on specific mutations that drive the growth of a patient's tumor cells, thereby enhancing the chance of a successful treatment response without the side effects of chemotherapy or radiation. However, this sophisticated mechanism of action also means that these drugs are only effective in those patients whose tumors carry these mutations. Therefore, the success of these personalized or precision medicine treatments depends on accurately identifying patients with a particular mutation before treating them with the appropriately matched drug. This is why the sophisticated new diagnostic tests that enable physicians to match the right drugs to the right patients play such a critical role in cutting-edge cancer care.

Importance of Accurate and Effective Diagnostics in Cancer Care

That over 40 targeted cancer therapies have gained FDA approval over the past 10 years is a testament to the fact that we have a streamlined and effective regulatory process in the U.S. To ensure that the right patients receive a targeted drug, the FDA approves targeted therapies in

¹ US Food and Drug Administration. Hematology/Oncology (Cancer) Approvals; accessed on Sep. 5, 2014 <http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm>

conjunction with a diagnostic tool called a *companion diagnostic*, which provides physicians and patients with information that is essential for the safe and effective use of the therapy². Drugs that are effective in a specific sub-population of patients are approved with the stipulation that the corresponding diagnostic test must be used to identify the appropriate patients for treatment. Thus, it follows that the diagnostic tools used to detect the molecular alterations that form the basis of tailored or personalized cancer treatments are crucial for the safe and effective practice of personalized medicine. A safe, reliable, accurate, and sensitive diagnostic test is as important as a safe, reliable, and effective drug.

Different Paths to Market for Diagnostics

In contrast to the single regulatory path to market for drugs, there are two very different paths to market for a diagnostic³. The first path is by gaining approval or clearance from the FDA which requires a sponsor to demonstrate proof of analytic and clinical validity as well as clinical utility of the test in some cases. *This is the path by which companion diagnostics are currently approved, in conjunction with approval of a targeted therapy.* The second path to market is when a test developer designs, manufactures and offers the test within a single laboratory as a laboratory developed test or an LDT. Because LDTs are not subject to the same level of scrutiny as diagnostics approved through the first regulatory path, there is less certainty and confidence in the accuracy of these products. This is particularly relevant for the highly sophisticated DNA sequencing technology based tests that generate the information from tumor cells that form the basis for many companion diagnostic tests.

² US Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools); accessed on Sep. 5, 2014

³ Sawyers CL, and van 't Veer, LJ. Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research. Clin Can Res; Published Online First September 9, 2014; doi: 10.1158/1078-0432.CCR-14-2295.

For a cancer patient, the consequences of an incorrect treatment recommendation made on the basis of a faulty diagnostic test are unacceptable, since the patient may lose the opportunity to receive an effective treatment or may be exposed to side effects from a treatment that has little to no chance of benefit. Physicians and patients must be able to trust the claims made by developers of health care products, especially products that determine the treatment regimen for a cancer patient.

A Single Regulatory Standard to Ensure Patient Safety and Reliability of Diagnostics

Given the importance of diagnostic tests to personalized cancer treatments, the AACR believes it is imperative that all diagnostic tests used to make high-risk treatment decisions, including the tailoring of an individual's cancer treatment regimen, must be FDA-approved to ensure that these diagnostic tests are held to the highest regulatory and approval standards⁴. Having a single, strict regulatory approval standard will reassure the American public that the tests used in high-risk health care decision-making, regardless of origin, are safe, accurate, and effective.

The FDA's Proposed Framework for Regulatory Oversight of LDTs

The AACR welcomes the recent notification to Congress by FDA of its intent to phase-in a risk-based framework for regulatory oversight of laboratory developed tests⁵. We commend the FDA for taking a regulatory approach that puts patients first by proposing a classification of LDTs

⁴ Sawyers CL, and van 't Veer, LJ. Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research. Clin Can Res; Published Online First September 9, 2014; doi: 10.1158/1078-0432.CCR-14-2295.

⁵ US Food and Drug Administration. Notification to Congress and 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); accessed on Sep 5, 2014
<http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407409.pdf>

based on the risk posed by the test to the *patient*. We also note that the FDA plans to focus its efforts and appropriately utilize its resources by continuing to exert its policy of enforcement discretion over low-risk and routine laboratory procedures such as blood and urine analysis. As an organization of cancer scientists and physicians, we strongly support efficient and evidence-based regulatory policy making, and we look forward to doing the same with this proposal.

The proposed framework strikes a thoughtful balance between protecting patient safety while promoting research and innovation in this rapidly evolving field in the following ways:

- By prioritizing FDA's initial oversight efforts to ensure that high-risk LDTs undergo pre-market review to assess the accuracy and safety of the test especially when there is an FDA-approved/cleared equivalent currently on the market;
- By ensuring that this proposal will not adversely affect the ability of researchers at academic medical research centers to develop new tests or conduct clinical research;
- By ensuring that patient access to tests that have not yet undergone FDA review will not be obstructed in cases where there is not an equivalent FDA-approved or cleared test
- By requiring adverse event reporting of LDTs and
- By providing adequate time for laboratories and providers to be in compliance by phasing in the requirements over a period of nine years after the guidance is finalized.

Conclusion

Diagnostic tests are evolving to become more technically complex, and the complexity of these tests will only grow with the increasing use of next-generation sequencing or NGS-based tests. Further, clinicians are increasingly relying on these complex test results to make treatment

decisions. Therefore, patients and physicians should be confident in the test results that are forming the basis of high-risk treatment decisions, whether these tests are developed as an LDT or are kits approved by the FDA. Implementation of a risk-based framework by the FDA that would provide for evaluation of all high-risk molecular diagnostic tests would balance the need for encouraging innovative medical product development with the need for ensuring patient safety. Having a predictable and reliable regulatory environment is important for patients and for developers of diagnostic and drugs, since the success of a targeted therapy is inextricably linked to the successful development of its companion diagnostic test. Therefore, a single regulatory standard for high-risk diagnostic tests is crucial to ensuring the safety and efficacy of molecular diagnostic tests and the key to advancing personalized medicine. We are in the midst of an extremely promising age of innovative new cancer treatments. Genome sequencing and targeted treatments are revolutionizing the way we treat cancer patients and the way we develop cancer treatments. A robust, predictable, and reliable evidence-based regulatory framework will ensure that these 21st century cures will reach patients in an efficient and expeditious manner.

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About the American Association for Cancer Research

Founded in 1907, the American Association for Cancer Research (AACR) is the world's oldest and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 35,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and cancer advocates residing in more than 90 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis, and treatment of cancer by annually convening more than 20 conferences and educational workshops, the largest of which is the AACR Annual Meeting with more than 18,000 attendees. In addition, the AACR publishes eight peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as

well as in cooperation with numerous cancer organizations. As the scientific partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit www.AACR.org.

Mr. PITTS. The Chair thanks the gentleman.

Thanks to all the witnesses for your opening statements.

I have a unanimous consent request. Submit for the record a letter dated September 8 from the Combination Products Coalition. Without objection, that will be entered into the record.

[The information appears at the conclusion of the record.]

Mr. PITTS. I will begin the questioning, and recognize myself 5 minutes for that purpose.

Mr. Fish, we will start with you. I have heard companies and past witnesses remark that regulatory uncertainty and a lack of incentives in the diagnostics space have contributed to innovative products sitting on companies' shelves. Do you believe this guidance document would address these issues or create more regulatory uncertainty?

Mr. FISH. Mr. Chairman, we believe that this proposed framework by the FDA would help reduce the current uncertainty in diagnostics by ensuring similar review for tests that present a similar level of risk, and make it clearer for both laboratories and manufacturers alike what the path forward is to provide the clinical diagnostics to patients. So in our view, we believe this would help address the stifling of innovation we see under the current system.

Mr. PITTS. Mr. Mertz, you state in your testimony that enhancing CLIA may be the way to go. CMS, the agency that implements CLIA, recently stated, "CLIA does not address the clinical validity of any test, that is the accuracy with which the test identifies measures or predicts the presence or absence of a clinical condition or predisposition in a patient. On the other hand, FDA does." CMS has clearly indicated that it does not want, nor could it handle, additional testing responsibilities authority in this area. Why are you still proposing it?

Mr. MERTZ. Thank you. And we have known over the years that CLIA has taken the position that they do not regulate clinical validity. We actually believe under their statutory authority that they could, and the regulations on CLIA actually touch on that. They are required the clinical accuracy of the test, the performance of the tests are regulated. However, because there is this perceived gap that they do not regulate clinical validity, we have been very supportive for many years for modernizing CLIA, for strengthening CLIA so that it would specifically require CLIA to look at the clinical validity of all new laboratory-developed tests. We were supportive of Congressman Burgess' bill, the Modernizing CLIA Act, which would specifically have an approval process for all new laboratory-developed tests, not just a few that the FDA will be able to look at, but they would review the clinical validity of all new laboratory-developed tests.

In addition, I would touch on the resource issue that has been talked about today. The FDA is supported by—20 to 30 percent of their funding is from the user fee. They only approved 23 tests. CLIA actually is funded 100 percent by a lab user fee, and a GAO report from a couple of years back indicated that they had \$70 million in carryover money they hadn't spent. They have a lot of resources there that they could use. The other thing is they—CLIA would not have to—FDA is proposing to duplicate all of the things underlying looking at clinical validity. They will have new inspec-

tions, new registration, licensing, labeling, all these things will be done a second time. You could very surgically, with CLIA, go in, add that clinical validity requirement, have adverse reporting, and it would be fully funded by the laboratory industry with the funds that we provide in the user fee. So we think that would actually be a much more effective way to guarantee the safety of these tests, and establish the clinical validity of them.

Mr. PITTS. Thank you.

I have a couple of questions for each of you. So regardless of whether you agree or disagree with the substance of the guidance, do you believe it would be a significant shift in longstanding Agency policy and a departure from existing practice for the regulated industry?

Mr. Fish, we will start with you. Just go down the line.

Mr. FISH. So we concur with FDA's assessment that this framework would represent a change in practice by the Agency, but not a change in regulation. Since the FDA is essentially not proposing to change any current regulation that applies to diagnostics, but simply to extend its enforcement of those regulations to laboratory test developers. So we share that opinion with FDA.

Mr. PITTS. OK, and you can answer yes or no if you would like. Do you believe, Dr. Behrens Wilsey, that it would be a significant shift in longstanding Agency policy, and a departure from existing practice for the regulated industry?

Ms. BEHRENS WILSEY. The Coalition does think it would be a significant shift and change in long-term policy, but that is the reason why we believe many of these questions need to be answered in advance to finalizing guidance.

Mr. PITTS. Mr. Mertz?

Ms. BEHRENS WILSEY. And we think if that were the case, that it would go to resolving a lot of the issues.

Mr. PITTS. Mr. Mertz?

Mr. MERTZ. We do think it would be a completely substantial shift in what they have regulated. From the time that the device amendments were enacted in 1976 until the early '90s, they never said anything about regulating laboratory-developed tests, even while CLIA was being enacted in '88. There was no mention in Congress, in FDA. They asserted absolutely no authority over laboratory-developed tests for 16 years after the Device Act, and there were many, many hundreds of LDTs being created at that time. So we think this is a significant shift in their policy.

Mr. PITTS. Dr. Newton-Cheh?

Dr. NEWTON-CHEH. Yes. This would be an important and significant shift in the practice of the FDA, exercising enforcement discretion, and it is welcome.

Mr. PITTS. Dr. Sawyers?

Dr. SAWYERS. I would take a slightly different take. I don't think it is a shift in the sense that companion diagnostics have been a standard part of the approval of targeted cancer drugs now for about 8 to 10 years. I think the shift, of course, is expanding that to LDTs that are measuring the same thing, but not subject to the same regulation.

Mr. PITTS. All right, and then the second question, we can go in the reverse order. Dr. Sawyers, do you believe FDA should establish a new framework of this nature by guidance or regulation?

Dr. SAWYERS. I think guidance would be the start to get it right, as Dr. Shuren pointed out, through dialogue, and then I think it should move to regulation.

Mr. PITTS. Dr. Newton-Cheh?

Dr. NEWTON-CHEH. I think the FDA's use of guidance is consistent with its past practices and its open to public comment seems acceptable.

Mr. PITTS. Mr. Mertz?

Mr. MERTZ. Well, we question and challenge their statutory authority to even do guidance or regulation in this area. However, if they were to proceed, it definitely should be done through notice and comment rulemaking.

Mr. PITTS. Dr. Behrens Wilsey?

Ms. BEHRENS WILSEY. I am not an attorney and so I am not going to comment on FDA's authority, but I will say that the Coalition believes that guidance could be an effective tool if used properly and exercised properly.

Mr. PITTS. Mr. Fish?

Mr. FISH. As FDA has noted, it is not proposing to change existing regulation, but simply to enforce it with respect to LDTs, and we concur with that assessment.

Mr. PITTS. Thank you.

The Chair recognizes Mr. Green 5 minutes for questions.

Mr. GREEN. Thank you, Mr. Chairman, and thank our witnesses for being here.

We have heard a great deal about the boom of innovation in LDTs since Congress enacted the Medical Device Amendments in 1976. Over the last 4 decades, like many areas in medical innovation, the products used in patient care have significantly grown and evolved. When there are revolutionary advancements in health products, a new oversight framework tailored to the specific type of device or product may be warranted. Patient safety cuts both ways, ensuring a product is safe and effective, and also ensuring fostering innovation so clinical care improves over time. Since 1976, LDTs have evolved from being limited in number and relatively simple tasks primarily used to diagnose rare diseases and conditions. Today, they have increased in number, complexity, and accessibility.

I understand that nearly all FDA-approved and FDA-cleared test kits began as LDTs. Some of the innovation we have seen in LDTs base from labs developing new tests or modifying existing tests to meet patient needs. Yet, as the complexity and accessibility of highly sophisticated tests have grown, there is a need to promote continued innovation, while recognizing the risk of LDTs posed to patients is much greater than in the past.

Mr. Fish, we have heard concerns that FDA oversight will stifle innovation for tests that are for rare diseases, and will slow patient access to new tests. Can you provide a response to these concerns, and how the FDA proposes to address this?

Mr. FISH. Well, I think we recognize that any regulation comes with a burden, and we think the appropriate question is not wheth-

er or not there is a burden associated with regulation, but whether there is a rationale for that regulation and whether the burden is commensurate with a public health issue. And our feeling is that FDA is seeking to achieve, and largely is achieving through this framework, a balance between additional enforcement of regulation with respect to LDTs, and continued enforcement discretion. FDA has pointed out, I think pretty clearly in its framework, that with respect to a number of different categories of LDTs and settings in which LDTs are both developed and used, that it will continue to exercise enforcement discretion, thereby allowing LDT innovation to continue to flourish and serve patients in those settings.

Mr. GREEN. OK. Mr. Mertz, I understand that once a test kit is FDA approved and enters the market, the laboratories may modify the kits, which is in many cases expanded uses that even improve tests.

Can you speak to this, and how does the FDA proposal impact this practice?

Mr. MERTZ. Yes, thank you. And this is one of the areas we are very concerned about because, as has been pointed out, most of the LDTs, 1,000 or so new LDTs a year, most of them are created because there is no FDA-approved kit, and the patient needs the test and there is no kit. For many others, most of the rest if there is a kit that was originally LDT, now it is an approved kit by the FDA, but it actually needs modifications in order to have it keep up with technology. And interestingly, the one example that Dr. Shuren said earlier was sort of a copy of a kit that was being used. He was actually referring to the BRAF test for melanoma patients, and he said the labs claim it was better. Well, in fact, if you look at the testimony by the AMA, in fact, the FDA-approved kit turns out that, because it was frozen in time, you have an approval process and that technology is frozen in time, that test cannot distinguish between two different mutations for melanoma, and the AMA pointed out the clinicians, they actually must know that the specific mutation, and really to detect the right mutation and to have the right treatment, they have to use the LDT modification of the BRAF test.

We see many, many other cases of this where the original HIV test back in 1987, which was approved still has not been updated. It is the LDT that has served for 25, 30 years now because that technology was frozen in time. So really the FDA-approved kit actually never was the standard of care. And this is actually what most LDTs are either unmet need or they have actually made some change that is absolutely essential to clinicians in treating a patient.

Mr. GREEN. Do you believe that there should be premarket review of LDTs to ensure their safety and effectiveness?

Mr. MERTZ. Well, first of all, actually what the FDA is proposing is—in the case of high-risk LDTs is not premarket approval.

Mr. GREEN. I know, but would you go as far as—

Mr. MERTZ. OK, but in terms of our position—thank you. First of all, as I said before, we believe that the clinical validity of the test should be established. That is generally done within the lab, through the reviews of the crediting organizations, but to make it absolutely clear that it is, we supported legislation that would add

that requirement under CLIA to require all new laboratory-developed tests, all 800 or 1,000 a year there are, to go through an approval process at CLIA to establish the clinical validity. So yes we do, but we think that would be a much better way than doing it than duplicating CLIA again under FDA, and putting a much more burdensome process that will make it really, really untenable for most tests to go through that process.

Mr. GREEN. Thank you.

Mr. Chairman, I have one more question, if I could ask?

Mr. PITTS. Go ahead. Proceed.

Mr. GREEN. Mr. Fish, some of your fellow panelists have raised questions about whether the FDA has the authority to regulate LDTs, suggesting that LDTs are more akin to services provided by physicians than devices. I would like to ask your views. We heard today, Congress amended the Federal Food, Drug, and Cosmetic Act in 1976 to give the FDA authority over in vitro diagnostics, IVTs. Can you describe what the differences are, if any, between FDA-regulated IVTs and so-called laboratory-developed tests, and how do you respond to the claim that LDTs are not subject to FDA jurisdiction?

Mr. FISH. Well, first of all, as you note, the statute clearly refers to medical devices as including in vitro diagnostic products, which are the equipment and materials used to produce in a test. Our view is that LDTs are the same as diagnostics produced by a manufacturer. The question of whether or not LDTs are solely services I think obscures the fact that when a laboratory performs a test, there is still a test at the heart of what it performs, analogous to a doctor's office or a medical center providing chemotherapy. There is a service provided in the application of chemotherapy for a patient, but there is still a drug at the center of what is being performed as a service. So our view is that LDTs, from a practical standpoint, still constitute a regulated article under the Medical Device Amendments, and FDA has made that case and we concur with it.

Mr. GREEN. Thank you, Mr. Chairman, for your courtesy.

Mr. PITTS. The Chair thanks the gentleman.

I now recognize the Vice Chairman, Dr. Burgess, 5 minutes for questions.

Mr. BURGESS. Thank you, Mr. Chairman, and I do thank all of our witnesses for being here today. It is an important topic that we do need to discuss.

Dr. Behrens Wilsey, let me just ask you a question about something that could affect, say, the off-label use of a diagnostic. If you have a manufacturer-distributed test, the laboratory can use the test off-label in the practice of laboratory medicine, and that is not going to upset the FDA. But with a laboratory-developed test, if the FDA considers the laboratory to be a manufacturer, and considers the LDT service to be a device subject to the FDA's labeling rules, this could raise concerns that the laboratory is promoting off-label use.

From your perspective as an investor in laboratories performing laboratory-developed tests, how would this risk impact your decision to invest in a particular company?

Ms. BEHRENS WILSEY. Thank you. I appreciate this question.

This is a concern that the Coalition raised several years ago, and has discussed with the Food and Drug Administration, and the question that came up a little bit earlier today, and we greatly appreciate Dr. Shuren's assurance that this issue would be resolved reasonably. However, what I would say, the longstanding practice of labs consulting with physicians about patient management based on the results of the test is actually a requirement under CLIA. And at the same time, if labs become manufacturers under FDA regulations, depending upon the label and the physician use of the information, the lab consultation could be considered off-label promotion. And what we believe needs to occur is we need to wrestle down specifically what precisely would constitute a consultation, and what would precisely constitute off-label promotion, or else there is no question that, as an investor, that would chill investment in this area. That would be of great concern to investors.

Mr. BURGESS. Let me ask you a question. Mr. Mertz, I think, referenced the disparity between the number of tests and the number of approvals. From the investment perspective, I am not a lawyer, I am not an investor, I am a physician, I simply live downstream from all of this, but from the investor perspective, what does that do when you are looking at whether or not to put money into one of these products, the vast number that are available, the few that have been approved through the FDA, if there is a furtherance of the FDA's reach into this area, what is that likely to do?

Mr. MERTZ. So—

Mr. BURGESS. Dr. Behrens Wilsey.

Ms. BEHRENS WILSEY. I apologize.

Mr. BURGESS. Yes.

Ms. BEHRENS WILSEY. I—

Mr. BURGESS. From the investor's perspective, this discrepancy between number of tests coming around and the number of approvals, if the FDA's grasp is indeed increased, what does that do to the viability from the investor community?

Ms. BEHRENS WILSEY. We are very concerned about the number of tests. I was running out of time in my oral comments so that I didn't cite the same numbers that were provided by ACLA.

Having said that, we are very concerned. What would concern me as an investor is that you would create a very long line and a very protracted period of time in which these tests would have to go through the regulatory process. That absolutely would diminish interest in investing in this area.

Mr. BURGESS. And some of the financial return from a laboratory-developed test is de minimis when you compare it to a blockbuster pharmaceutical, is that not correct?

Ms. BEHRENS WILSEY. Absolutely. I made the point earlier that the two most important issues affecting investors in financing companies that develop these types of tests are regulation and reimbursement. And the quantity of evidence and the time in which you are required to develop that evidence so that you can provide it for the purposes of an FDA approval substantially lengthen the period in which you might generate some sort of a return. Actually, it substantially generates the period in which you have any hope of even getting reimbursed. So that is a great concern, and one of the rea-

sons why this area does not have the same number of investors as the pharmaceutical area.

Mr. BURGESS. Mr. Mertz, I appreciate your comments about the legislation introduced in the last Congress. I haven't planned to reintroduce it yet, just with that caveat, but when President Obama was Senator Obama and he introduced the bill that I put into the record this morning, the concept was the harmonization between CLIA and the FDA. Do you think that the bloom is off that rose, has that hour now passed and we are into a different realm where that is no longer possible?

Mr. MERTZ. No, and just interestingly, I was at ACLA when Senator Obama introduced that, and it was in reaction, in part, to what the FDA was proposing on an earlier iteration of this guidance, the IVDMA. They were going to regulate some of the LDTs, and it was in reaction to that and a much more measured approach which would rely on CLIA. But I don't think it is too late to do this with CLIA. As we heard earlier, it is going to take the FDA 9 years to recreate all of this regulation within their realm. So, no, I think—and they could ramp up much more quickly at CLIA because they have the foundation.

If I could, Congressman, quickly on the investment issue. Of the many hundreds of new LDTs a year, some of them are created by small startups, they are investor-funded, but hundreds and hundreds of them are created by academic medical laboratories. There is a letter that the—that you have and the committee has from 23 of the most esteemed medical institutions in the country, the Harvards and Stanfords and all of them, and they are very concerned. They said FDA regulation of LDTs would stifle innovation and be contrary to public health. So they are not really funded by investment capital. The Mayo Clinic, which is one of our members, they create over 100 new laboratory-developed tests a year, and they are worried that they are not going to be able to innovate. It is not even an investment capital issue.

Mr. BURGESS. OK, thank you, Mr. Chairman. I yield back.

Mr. PITTS. The Chair thanks the gentleman, and now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for questions.

Mr. WAXMAN. Thank you, Mr. Chairman.

I don't hear anybody on the panel argue that there shouldn't be a very careful scrutiny of these tests. It seems like the question is who should do it; CLIA or the FDA, and I don't think CLIA has the kind of expertise that we see at FDA.

Dr. Sawyers, you note in your testimony that we have been able to shift from classifying cancers by their site of origin in the body, to classifying them by their molecular subtype. I think this exemplifies the kinds of advances we need to capitalize on to further develop into targeted therapies for personalized medicine, and to speed new treatments to patients. However, we also see what was described in a 2011 New York Times article as a mini gold rush of companies trying to market tests based on the new techniques, at a time when the good science has not caught up with the financial push.

Mr. Chairman, Mr. Chairman, I would like to insert into the record that article from the New York Times dated July 7, 2011.

Mr. PITTS. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. WAXMAN. Thank you.

Dr. Sawyers, as you note in your testimony, the success of a targeted therapy is inextricably linked to the successful development of its companion diagnostic test. You also note that implementation of FDA's risk-based framework would balance the need for encouraging innovative medical product development with the need for ensuring patient safety.

Could you describe some of the harms you see from exempting lab-developed versions of these tests from FDA oversight, and some of the benefits you see from having them subject to FDA oversight? And as part of your answer, could you address whether you think FDA oversight will unnecessarily limit patient access to the best new tests?

Dr. SAWYERS. OK, well, I think that the benefit of having more oversight would be more confidence in what I will just call the me too tests that develop shortly after the approval of a companion diagnostic. The details of what the regulatory requirement for approval of those second generation tests is an important detail. It can't be such a high bar that it impairs or harms second followers from joining in, but I see that this next generation cancer drugs develop in a similar way because there is a clear set of guidelines and developers know what they need to do.

I also want to make a point about the ability to compare test results across different centers and across even the world. A point I made was that cancer is now subdividing into hundreds of diseases, and so one medical center running an LDT in that clinical lab can't easily compare the results from other labs. So a more uniform sort of trust in the sensitivity and specificity of tests would accelerate the post-approval understanding of what patients are most likely to benefit from what drugs.

In terms of harm, the examples have been given earlier of tests that didn't hold up to the light of day later on in subsequent publications, as made by my colleague in cardiology in his oral statement.

Mr. WAXMAN. Well, Dr. Newton-Cheh, do you want to comment on the question I asked or what Dr. Sawyers had to say?

Dr. NEWTON-CHEH. Yes, I think—I mean by way of example, the American public has by and large supported FDA's regulation of pharmaceuticals. They would not support rolling back to 19th Century Wild West where snake oil is indistinguishable from safe and effective therapies, and I think by the same token, they would not accept continuing unregulated LDTs in the 21st Century. I think to draw the—

Mr. WAXMAN. Why should FDA regulate it as opposed to CMS?

Dr. NEWTON-CHEH. I think that is what FDA does. I mean FDA has structures in place with expert advisory committees, and consultation with stakeholders evaluating clinical claims, evaluating the literature. That is the business that they have been in, so I see testing as another component of clinical validity. I think CLIA historically has been focused on the laboratory structures, the certifications, the personnel, and the precision of the measurement of

some biologic entity, but not necessarily the interpretation or application to medical therapy.

But if I could also draw a distinction between oncology where tissue is obtained, a molecular specificity is observed, and a therapy is targeted to that molecule. Well, that is a greater degree of precision than exists for cardiovascular disease. The two big killers are cancer and cardiovascular disease. Cardiovascular disease does not have such a precisely defined molecular understanding, and so there is, I think, a potentially greater harm for misapplying the inferences that are gained in oncology, where it has really been revolutionary, and I would say in cardiovascular disease it is about 10 years behind, and much of the claims that are currently out there for genetic testing to predict response to therapies are just unsupported.

Mr. WAXMAN. Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman.

I now recognize the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions.

Mr. BILIRAKIS. Yes, I guess it is working, OK.

Mr. Mertz, some here are saying that the FDA's intervention over laboratories is necessary to "level the playing field." However, your testimony lays out that laboratories are already regulated by CMS, and have been for decades, and that the FDA's actions may duplicate regulations rather than streamline them. Can you talk about the overlapping regulations and the problems that they could create?

Mr. MERTZ. Yes. Thank you, and I appreciate the question.

And some of those who make that argument that it is unregulated, it is actually a bit of a myth because maybe I can just describe it best in an example. One of my academic institutions, it is a big hospital and a lab, and they told me that the lab is actually—they consider it probably the most regulated part of the entire hospital, and others in the hospital look at the lab as being quite highly regulated.

The other point I want to make is that a manufacturer and a laboratory service are very different, and I think a good example of that that people understand is that a laboratory-developed test is not a product, it is not an article, it is not a machine. Most pap smears historically are laboratory-developed tests, and this is where a specimen is taken from the patient, a slide is prepared, a cytologist looks at the slide to detect cancer. If it is positive, it will be reviewed by a pathologist. Then they make a determination, give it to the OB/GYN, and that is a laboratory-developed test, and it could be considered—there is some risk involved if that diagnosis is wrong. I don't think many people would consider that procedure and that knowledge, and all of the physician involvement I just described, as a physical product that is sold commercially by a manufacturer. So that is not a manufactured product, it is a process. So that is regulated as that. So we are regulated, they are regulated. We are fundamentally different. If you look at the regulations under CLIA, labs, they do, they regulate them as labs. The personnel, the procedures, the specimen collection, the accuracy of the test, which is very important. You look at manufacturers, it is more about quality systems and the manufacturing process. It is a very

different process. But adding a whole second layer or a third regulation to laboratories is not leveling the playing field, it is making two different playing fields. It would make it very difficult to innovate, very expensive to innovate, and I would point out to others here that have brought up cases that—the KRAS test for colorectal cancer, there was—there has been—there was no test for 10 years for colorectal cancer until KRAS came along. The BRC for leukemia, that was a laboratory-developed test originally. A lot of them were laboratory-developed tests. So we are sort of playing on an entirely different field. We are regulated, and by adding another layer of regulation on top of labs is only going to stifle innovation.

And finally, there are ways if clinical validity, we agree it needs to be addressed, you could add that to CLIA without duplicating the rest of the playing field.

Mr. BILIRAKIS. Very good.

Thank you, Mr. Chairman, I appreciate it. I yield back. Thank you, sir, for your testimony.

Mr. PITTS. The Chair thanks the gentleman.

I now recognize the vice chair of the full committee, Mrs. Blackburn, 5 minutes for questions.

Mrs. BLACKBURN. Thank you, Mr. Chairman, and I thank each of you for being here, and I thank you for your patience. We appreciate that you are willing to come in and talk with us.

We are focused on 21st Century Cures on medical innovation, and as I said earlier with Dr. Shuren, how do we preserve access to affordable health care for all Americans, because right now, the price is going up, the networks are narrowing, and it is becoming more difficult for so many individuals in so many parts of the country to get that access they want.

Mr. Fish, I want to come to you and stay pretty much with where Mr. Bilirakis is. Looking at how the diagnostics are approved the same as the medical devices, and I have heard from a lot of your AdvaMed Dx members, and they feel like this should be approached differently, that the test should be approved and the diagnostics should be treated differently than medical devices. So do you support your members' position in that they should be handled differently?

Mr. FISH. AdvaMed Dx's position currently is that we are comfortable with FDA's current regulation of diagnostics. I think one of the issues that has been recognized is that the diagnostics are different than other medical devices, and FDA I think has recognized that in terms of the kind of data and information that it requires to be provided to approve those diagnostics as safe and effective, but we are currently comfortable with the existing regulatory system. I would say, furthermore, we thank the committee for its 21st Century Cures Initiative, and as we always have in the past, if the committee is interested in exploring further any ideas around FDA's ongoing or changing regulation of diagnostics, we would be very pleased to work with the committee on that.

Mrs. BLACKBURN. Great, thank you.

Dr. Behrens Wilsey, I want to come to you. I appreciated your comments in your testimony so much. Let me ask you this. You heard Dr. Shuren, and if you were providing guidance to the FDA as to how they were going to approach their regulation, trying to

get some regulatory certainty into the process, if you were to talk to them about reining in some of the mission creep that exists there, and also the LDTs, if you were talking to them about the LDTs and how that has impacted health care costs, what would you say to them?

Ms. BEHRENS WILSEY. We would like to encourage greater dialogue, as I mentioned earlier, before finalization of the guidance, in part, because there has been such a long period of time in which there has been enforcement discretion, because this would encourage more dramatic changes in this area, and because this area is really not just exciting technologically, but the potential applications now of the use of these technologies, not just by good actors but all actors, are becoming increasingly clearer and very important for the patient. So what we would really like to see, and what we would encourage by the FDA, is to work through greater levels of some of the details that would lay out in advance of any finalization of guidance, some of the very specific questions, many of which have been raised today in our discussion, so that there is a lot less that is assumed by how the FDA will approach answering those concerns and those questions after guidance is finalized, because at that point in time, the clock starts ticking. At that point in time, companies' investors, everyone begins to risk the progress and the opportunity for these types of technologies, so that the lack of certainty and the judgments that would occur after that are far less clear than what we think could occur between now and finalization of guidance.

Mrs. BLACKBURN. OK, thank you.

I yield back, Mr. Chairman.

Mr. PITTS. The chair thanks the gentlelady.

That concludes this first round. We will go to one follow-up per side.

Dr. Burgess, you are recognized 5 minutes for a follow-up.

Mr. BURGESS. Thank you, Mr. Chairman.

Dr. Behrens Wilsey, just before we leave that concept of guidance and guidance versus regulation, you heard Dr. Shuren's response to my question, are we going with guidance because regulation actually triggers a response from the Office of Management and Budget as to the financial impact. So I guess this is part of the problem. Why are we here talking about a regulatory guidance that apparently has been in the making since either 1976 or 2006, it is hard to follow, if the onus is so severe, why not proceed through a regulatory pathway, through that more established pathway, and let us do the economic analysis that I think, certainly from the investment community, I think you would welcome that, would you not?

Ms. BEHRENS WILSEY. Independent of rulemaking versus the guidance process, I would say that you could accomplish the same goal through both mechanisms. One important distinction being, of course, in rulemaking, the Food and Drug Administration has to respond to certain questions. On the question and the issue in the matter, I should say, of economics, I think that is an important question for everyone, whether FDA generates the numbers or collaborates with others in generating those numbers, those are still very important considerations. In fact, we have discussed whether

we could put our hands on numbers that could be helpful through this process. So I would say independent of the process, we would encourage assessment on the economics.

Mr. BURGESS. But the economic assessment may be circumvented by the fact that it is done through guidance rather than through regulation. That was my point—

Ms. BEHRENS WILSEY. I understand that.

Mr. BURGESS [continuing]. In the earlier question.

Ms. BEHRENS WILSEY. The distinction that I am making is that if FDA works through a reasonable process, in our opinion, they could perhaps not precisely end up in the same position as everyone would like them to through rulemaking, but we could certainly come much closer to that. Economics being one of the considerations.

Mr. BURGESS. Well, unfortunately, they may have given themselves some enforcement discretion on their own purpose.

Mr. Mertz, let me just ask you a question. It has come up several times on the issue of scalability at the FDA, and this—

Mr. MERTZ. I am sorry?

Mr. BURGESS. Scalability—

Mr. MERTZ. Yes.

Mr. BURGESS. We are talking about a very broad expansion into an area that is large and growing, and I think I heard you voice a concern are they actually ready to do this, and I have that concern and I asked Dr. Shuren and he assured me that they would, but realistically, as part of the Cures Initiative we have heard from people saying, look, one of the big problems with the FDA is their information architecture is so archaic, they have stuff that is written on paper records that should be digitized and in the digital age. So, again, I would ask you, because it obviously impacts your association a great deal, do you think the FDA is ready for the scale of this undertaking?

Mr. MERTZ. No, and as we pointed out, and by the way, Dr. Shuren said we weren't part of the MDUFA III negotiations, in fact, we were one of the stakeholders, so we became very familiar with the process and how much funding they had.

As I mentioned, there are 11,000 complex labs, not 6,000. There are probably tens of thousands of laboratory-developed tests. We know that they only were able to look at 23 clear FDA-approved tests last year. Just the initial highest-risk tests they are talking about, we had heard some reports that they may look at 100 highest-risk tests within the first year or so. That would be a fivefold increase in the number of PMAs they would be doing in the first year. They have said there is no user fee, so they would have no additional money to do a fivefold increase in the number of PMAs. So we are concerned it would not only slow down innovation with LDTs, it could very well slow down the innovation in the FDA, the regular manufactured kits, so we are very concerned about that. We agree completely that the rulemaking would flush out the economic impact because until they define what high risk is, they won't know how many LDTs they are going to have to look at. Until you know how many LDTs you are going to look at, you have no idea what the burden is on industry or the FDA. So I think requiring them to do the economic impact would really force them to

say what they are going to regulate and how many LDTs there are, and then it will expose the impact it will have on the laboratory industry and the FDA.

Mr. BURGESS. Thank you, Mr. Chairman, and I will yield back.

Mr. PITTS. The Chair thanks the gentleman.

I now recognize the ranking member of the committee, Mr. Waxman, 5 minutes for a follow-up.

Mr. WAXMAN. Well, thank you very much, Mr. Chairman.

Dr. Sawyers, Mr. Mertz has testified if there were problems with LDTs, we would have more publicity about them. Do you agree with that? Would doctors and patients necessarily know if tests were not giving good advice for clinical decisions?

Dr. SAWYERS. Yes, I would disagree. I think it is possible because physicians are so busy and don't know whether the tests they have ordered is an LDT or an FDA-approved cleared test, that they may not know, and if there is no requirement for reporting back, how would we know? So—

Mr. WAXMAN. Yes.

Dr. SAWYERS [continuing]. I think it is an unknown.

Mr. WAXMAN. And, Dr. Newton-Cheh, how do you respond? Same question.

Dr. NEWTON-CHEH. It is completely opaque. I think the current environment for the practice of health care is increasingly complex, and I think physicians, patients, payers, they are all critical stakeholders here, I think they really rely on having independent evaluation of the claims that are associated with diagnostic tests.

Mr. WAXMAN. Thanks.

Mr. Fish, I would like to ask you a couple of quick questions. One often cited critique of FDA's proposal to oversee LDTs is that CMS, under its CLIA authority, should regulate these tests, not FDA. How do you respond to this, and do you think that CMS regulatory authority for LDTs should be the sole regulatory authority?

Mr. FISH. I think it is important to distinguish between what an ethical and competent laboratory currently probably does, as opposed to what CLIA actually requires, and as Dr. Shuren pointed out, what CLIA currently requires is vastly different than what FDA requires. CLIA requires that laboratories follow good processes and practices to ensure that their personnel are proficient, and that they have processes in place that ensure the good practices when they perform their tests, but FDA, on the other hand, requires a number of aspects of laboratory testing that are not present in CLIA, including premarket review and approval of tests, it requires that there be a demonstration not only of analytical validity but also clinical validity, in other words, is it meaningful to diagnosis, they require adverse event reporting and quality systems regulation, and all of these aspects are missing from what CMS does. And given the questions around what agency is prepared to regulate LDTs, I think the answer is no agency is conceivably as ready as FDA, and they—that is the appropriate agency to carry this out.

Mr. WAXMAN. Yes. Let me ask you about this claim about increased regulatory oversight stifling innovation. How do you respond to this claim? I know some members of your trade association, AdvaMed Dx, have had the experience of having obtained

FDA approval for their LDT, only to find that the next day a laboratory launches a copy of that LDT without undergoing FDA review at all. Please describe your views on the impact that this situation can have on innovation.

Mr. FISH. I would first point out that as a core matter, regardless of how this situation gets reconciled, the current uncertainty in having two very different paths to market for the same test is something that shouldn't stand as a matter of public policy, and it has ripple effects from a number of different standpoints. It has a ripple effect from the standpoint of investor certainty that we talked about, it has an impact on the competition that you just raised of LDTs coming out that purport to be the same as an FDA-cleared test, it has implications for clinician and patient transparency as well. So, again, regardless of the decision that is ultimately made, perhaps by Congress as well, this is just a situation that currently can't stand.

As far as innovation goes, FDA made a very important point when it said that it would not enforce regulations with regard to LDTs that are developed and used in the academic medical setting. Mr. Mertz referenced this letter that was sent by a number of leading academic medical institutions. Shortly thereafter, FDA came out with its framework and explicitly said we are not worried about the tests that are being performed in those settings, we are concerned about stand-alone, independent laboratories developing tests that are outside the context of patient care. And that is the test where FDA is concerned. So I think they acknowledged that innovation could continue on LDTs in the academic medical setting.

Mr. WAXMAN. FDA appears to be looking at prioritizing those tests with the greatest amount of potential harm to patients, and exempting a lot of other LDTs that might not be as serious. Do you think that is a reasonable way to prioritize the cases, or do you think there ought to be a rulemaking, every LDT ought to be subject to every test and every evaluation?

Mr. FISH. Well, I would first say, regarding rulemaking, if FDA were to proceed here by rulemaking instead of by guidance, there would be nothing new to say, it would simply say and you too, because the regulations already exist. So it is not clear that there would be any rule to put forth. And FDA, I think, is taking exactly the right approach. We have called for years for all diagnostics to be regulated under a risk-based approach to ensure that the burdens of regulation are commensurate with the risks presented by those tests.

Mr. WAXMAN. Yes.

Dr. Behrens Wilsey, I thought your last few statements have been very wise. It seems to me what you are saying is you want to see what FDA is going to do, you are afraid it could stifle innovation, but you think, handled the appropriate way, it might not stifle innovation at all, is that a correct statement?

Ms. BEHRENS WILSEY. Yes. I think even the improvements that we have seen in the proposed guidance—

Mr. WAXMAN. Yes.

Ms. BEHRENS WILSEY [continuing]. Between 2006 and today, we have already seen some improvements, and we certainly heard from Dr. Shuren earlier, willingness to hear more, so I think—

Mr. WAXMAN. Yes.

Ms. BEHRENS WILSEY [continuing]. If we proceeded down a path that allowed greater transparency, allowed the opportunity and the time for all parties to discuss the issues, and actually give some specific answers to some of the questions that have been raised, I think we would find ourselves in a very good position.

Mr. WAXMAN. Yes.

Well, Mr. Chairman, I want to commend you on this hearing. I think just having this open hearing and getting different views and hearing concerns can help FDA, can help everybody make sure that the right thing is done, because we don't want to stifle innovation, we do want these LDTs to continue, but we don't—and you certainly wouldn't want investors to put money into something that could end up doing nothing, and might even harm people. So let us hope that this process will continue at FDA and we will get a good result.

Thank you. Yield back my time.

Mr. PITTS. The Chair thanks the gentleman.

And on that note, that concludes the questioning at this time. Members will have follow-up questions. We will send them to you. We ask that you please respond promptly. I remind Members that they have 10 business days to submit questions for the record, and they should submit their questions by the close of business on Tuesday, September 23.

Very important, informative hearing. Thank you very much.

Without objection, the subcommittee is adjourned.

[Whereupon, at 12:25 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

PREPARED STATEMENT OF HON. FRED UPTON

Today marks the seventh Health Subcommittee hearing Chairman Pitts has convened as part of the bipartisan 21st Century Cures initiative. I would like to thank him again for his tireless work on this effort, including the exceptional roundtable he hosted in Lancaster, Pennsylvania, in late August that I had the pleasure to attend along with Ranking Member Pallone and Dr. Burgess.

Over August and the early part of September, members from both sides of aisle held roundtables across the country to solicit feedback on accelerating cures and treatments for patients. This really has been a collaborative effort, and we need everyone to continue providing us with specific ideas—none too big, none too small—about how we can make a significant reduction in the time and costs associated with the discovery, development, and delivery of safe and innovative new treatments and cures for patients who need them.

Personalized medicine has really been a recurring theme throughout this entire discussion. According to the Personalized Medicine Coalition, “While the potential benefits of personalized [medicine] are straightforward—knowing what works, knowing why it works, knowing whom it works for, and applying that knowledge to address patient needs—the intervening variables that determine the pace of personalized medicine’s development and adoption are far more complex. Among those variables are the laws and regulations that govern personalized medicine products and services used in clinical practice.”

Today’s hearing is an important opportunity to hear from a variety of stakeholders about just that. Particularly since the mapping of the human genome, diagnostics provide researchers and clinicians with valuable tools to match the right patients with the right course of therapy. We must ensure that our laws and regulations keep pace so that innovation in this space continues and patients benefit from accurate and reliable tests.

On July 31, 2014, FDA notified the committee that the agency intends to issue draft guidance to implement a new risk-based framework governing the review and oversight of laboratory developed tests. FDA has indicated for several years that it

planned on taking this step. Because it will have such a substantial impact on how these products and services are currently being used in practice, we required the agency notify the committee before moving forward. This provision in the Food and Drug Administration Safety and Innovation Act was not an endorsement of such an approach but recognition of the fact that a number of legal, procedural, and substantive questions about FDA's role in this complex policy area remained outstanding.

I thank Dr. Shuren and our other witnesses for their testimony about whether the agency has adequately addressed these issues and what role Congress can play in making sure that personalized medicine continues to flourish.

PREPARED STATEMENT OF HON. HENRY A. WAXMAN

In 1976, Congress first passed a law making it clear that FDA should ensure that diagnostic tests were safe and effective. At that time, FDA decided that tests developed and used by clinical laboratories, so called "laboratory developed tests" or "LDTs," did not warrant oversight. They generally were made in small quantities and were used by local labs. FDA opted to conserve its scarce resources by refraining from enforcing applicable medical device requirements against laboratories making LDTs. That was a policy that made a lot of sense at the time.

Today, things are quite different. As we move closer to achieving a new system of personalized medicine, practitioners are increasingly using LDTs to help make critical treatment decisions. Choices about which chemotherapies or medicines to administer-or in some cases, to withhold treatment altogether-are being made every day on the basis of LDTs.

Additionally, LDTs are no longer made in small local labs and used by physicians and pathologists working in a single institution responsible for a local patient population. FDA's enforcement discretion policy has become untenable as LDTs are increasingly manufactured by large, national laboratory corporations, contain sophisticated technologies and complex algorithms, and are distributed and used throughout the country.

I applaud the agency for finally taking formal action to change its LDT policy by issuing the notification of its impending guidance. It is a step that was long overdue.

One of the primary reasons this step is overdue is that there is currently a regulatory void surrounding these tests. The Centers for Medicare and Medicaid Services (CMS) oversees the laboratories that conduct testing, through the Clinical Laboratory Improvement Amendments (CLIA). But CMS does not evaluate whether the tests are clinically reliable. In other words, under FDA's enforcement discretion policy, no one is looking at LDTs to assess whether they accurately identify, measure, or predict the presence or absence of a disease or condition in a patient.

In today's world of highly sophisticated tests, that is a situation no American patient should tolerate. When a newly pregnant woman is given complex genetic tests to determine whether her unborn child is genetically predisposed to a serious disease or condition, she expects that the tests have been found to be accurate. Yet many of these tests are being marketed without any oversight from our scientific experts at FDA.

FDA is still in the early stages of its regulatory process, but from what I can tell, FDA is striking a reasonable balance. FDA is not proposing to oversee every LDT on the market. On the contrary, the agency is seeking to regulate only those LDTs that pose risks for patients if the tests are not clinically valid. And FDA is providing plenty of time and notice for companies marketing these tests to comply with any new requirements, most of which will be gradually phased in over the course of the next 10 years.

I hope today's hearing will allow our witnesses to exchange ideas about ways the draft guidance might be improved, including areas in which more detail could help answer questions about how FDA intends to oversee these tests and allay any concerns that have arisen. If useful suggestions are provided, I encourage FDA to consider them and take them into account as appropriate.

But concerns about whether FDA is the appropriate regulatory body to oversee these tests in the first place are not well-founded. I strongly disagree with those who would assert that FDA lacks jurisdiction over LDTs and that CMS alone should regulate them under its CLIA authority. These tests are a type of "in vitro diagnostics," that is, tests performed outside the body, for example on specimens taken from the body. In 1976, Congress amended the law to provide FDA with explicit authority to regulate in vitro diagnostics. Congress did not differentiate FDA's authority over such diagnostic tests based on what kind of entity makes them.

What is most important is the need for FDA involvement. CMS has stated that FDA is the agency with expertise in evaluating the clinical validity of these tests. CMS evaluates whether a particular test finds what it is supposed to find and whether labs conduct the test appropriately. But it does not evaluate whether what the test finds is clinically meaningful.

It makes no sense to suggest that CMS should somehow take on FDA's role over LDTs, while the FDA continues to oversee other medical devices. This would result in a staggering amount of bureaucratic duplication. That is not a wise approach for patients or taxpayers.

LDTs offer great promise to improve human health. But we need to ensure that the public is protected against unsafe or ineffective LDTs.

And that is why we should support FDA's proposal to take a more assertive regulatory stance over these tests. I look forward to hearing more from our witnesses on this today.



STATEMENT

of the

American Medical Association

for the Record

**U.S. House of Representatives
Committee on Energy and Commerce
Subcommittee on Health**

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

September 8, 2014

145

STATEMENT

of the

American Medical Association

for the Record

**U.S. House of Representatives
Committee on Energy and Commerce
Subcommittee on Health**

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

September 8, 2014

The American Medical Association (AMA) applauds the U.S. House of Representatives Committee on Energy and Commerce Subcommittee on Health's (Subcommittee) efforts to identify policies that will accelerate the development and wide-spread clinical application of 21st Century Cures. The AMA appreciates the opportunity to provide comments on the two central goals of this initiative—to encourage innovation and to embrace the rise of personalized medicine. The AMA shares the Subcommittee's focus on achieving better clinical care for patients, better health for our communities, and lower costs through cures driven by the unprecedented rate of clinically significant genetic and genomic discovery applied to medical practice. Given the impact that personalized medicine is already having and is expected to have on patient testing and treatment in the future, it is critical that applicable frameworks for oversight and policies for coverage and payment of laboratory developed tests (LDTs) support rather than undermine these goals.

In this statement, we wish to highlight the following:

- LDTs are a critical part of the practice of medicine, drive innovation, provide a critical safety net to combat outbreaks of infectious diseases and bio-threats, and often constitute the only test option for patients with rare diseases where a large commercial market does not exist.
- Clinical laboratories where LDTs are performed are currently regulated through federal, state, and, frequently, third party accreditation bodies.
- The AMA supports congressional efforts to provide a federal agency with the authority to assert greater oversight of laboratories for certain LDTs that the AMA has identified as high-risk—where incorrect results cause harm to patient and test methodology is not

transparent nor well understood (as in the case of tests that use complex algorithms to produce results, for example).

- The AMA questions the FDA's legal authority to regulate LDTs and, even if such authority exists, the significant changes proposed require notice and comment rule-making.
- The FDA's proposal as currently fashioned would prevent physicians from providing medical care that constitutes the most appropriate and clinically necessary care, severely limit patient access to life-saving tests, and slow innovation and integration of personalized medicine into modern medical practice.

We urge the Subcommittee to carefully consider that nearly all Food and Drug Administration (FDA) approved or cleared commercial test kits began as procedures—LDTs—in clinical laboratories regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). In fact, the number of FDA-cleared or -approved tests represents an extremely small set of tests relative to LDTs. In addition, the AMA urges the Subcommittee to consider the impact of recent highly disruptive policy changes to coverage by federal health care programs including Medicare, Medicaid, and the VA. The new policies have resulted in major confusion, loss of access among Medicare, Medicaid, and VA patients to tests that represent the standard of care, and have created ongoing instability. While the primary focus of today's hearing concerns the FDA's congressional notice and accompanying draft guidance documents proposing to impose new regulatory requirements on physicians developing and offering LDTs, careful consideration should be given to the tsunami of policy changes underway related to pricing and coverage that have already chilled and undermined efforts to accelerate 21st Century Cures in this space.

Laboratory Developed Tests: Overview

The current regulation of laboratories primarily under CLIA allow physicians from varied medical specialties such as pathologists, oncologists, infectious disease specialists, and medical geneticists to rapidly and safely develop, improve, and modify laboratory medical practice in response to new and validated medical findings, public health challenges, and the individual testing needs of patients. As noted above, the overwhelming majority of laboratory tests provided in the U.S. are LDTs in contrast to the very limited number of commercial kits cleared or approved through the FDA.

LDTs play an essential role in protecting the public health when there is an infectious disease outbreak, ensure the availability of diagnostic tools for rare diseases where a large-scale commercial market for kits does not exist, and accelerate innovation. LDTs also promote value, competition, and encourage the clinical application of patient-centric tests. Personalized medicine including the use of genetic tests and gene-based treatment modalities constitutes the practice of medicine. Given the training of physicians and their direct relationship to patients, physicians have a central role to play in the development of laws, regulations, and policies that impact the clinical implementation of personalized medicine, which includes genetic and genomic testing, the interpretation of testing within the clinical context, and identification of targeted therapies. Testing alone will not dictate patient treatment. Rather, a physician's clinical expertise, including developing, validating, and performing a test along with interpreting the test results in the context of the patient's condition and preferences, guide treatment options. The foregoing may frequently involve

the clinical expertise and judgment of a number of physicians and other highly trained medical experts. In short, physicians, patients, and LDTs are not widgets manufactured in a factory and shipped around the country. Instead LDTs reflect the highest level of clinical expertise, including education and experience of physicians tailored to specific patient medical needs.

LDTs Innovation Driver

Physicians have played a key role in driving the ongoing discovery and rapid application of research validated clinical findings to patient care. The Institute of Medicine and others have wrestled with the unacceptably slow rate of adoption into medical practice of research findings with relevant clinical use. In area of personalized medicine, physicians and laboratories developing and validating LDTs have dramatically cut the seven to fifteen year lag in the application into clinical practice. Increasing the regulatory burden and duplicating existing regulation would likely slow significantly what is currently an area of medicine where such lengthy delays have been diminished.

LDTs providing genetic and next-generation testing and screening have already become common in certain medical specialties. For instance, newborn screening is universal, and carrier, pre-implantation and prenatal testing is commonplace. These continue to improve with new discoveries and associated diagnostic/screening improvements. For example, prenatal screening for some chromosomal abnormalities can now be done noninvasively by examining fetal DNA circulating in the mother's blood. Other areas where genetic and next generation sequencing testing services and treatment have delivered game-changing results in clinical practice include infectious as well as rare diseases. The rapid translation of new medical information into clinical practice via LDTs has most notably begun a transformation of oncology. A number of academic medical centers have announced well-funded initiatives to develop the infrastructure for widespread adoption of genomic-based testing and treatment in oncology—and they are not alone. A large network of community-based oncology practices have also invested in the development of infrastructure that will propel adoption of personalized medicine as a standard of care in testing, risk assessment, and treatment.

In addition, it is important to highlight targeted therapeutics and companion tests. Targeted therapeutics, usually drugs or biologicals, are treatments designed to benefit a particular subpopulation, or whose use in another subpopulation might be especially disadvantageous or require different dosing. Companion tests are accompanying laboratory testing procedures and professional services identifying or measuring genes, proteins, or other substances that delineate the subpopulation that will derive benefit from the targeted therapeutic and yield important information on the proper course of treatment for a particular patient.

There are a number of examples that underscore this point, but tests for the BRAF mutation stand-out. BRAF is a specific gene that can mutate and can cause normal cells to become cancerous. This mutation is frequently found in the aggressive form of skin cancer called melanoma, which has a poor prognosis in advanced stages. The BRAF mutation has also been found in colon, ovary, and thyroid cancers. A treatment was developed to specifically inhibit the BRAF gene mutation when it is known to be the cause of the cancer. In 2010, a clinical trial was performed to treat patients with advanced melanoma using a traditional

drug or a BRAF inhibitor biological. The response rate to the BRAF inhibitor biological was 48 percent versus five percent with the traditional drug. At six months, 84 percent patients taking the BRAF inhibitor biological were still alive versus 64 percent of the patients receiving the standard treatment. In August 2011, the FDA approved for market the BRAF inhibitor biological for use in patients with a specific BRAF mutation, demonstrating how urgent the need was for this treatment. The key to the treatment of this deadly form of skin cancer is ascertaining whether a BRAF gene mutation is present in the patient's cancer cells. There are, however, different BRAF mutations, and treatment outcomes are impacted by which mutations are present, which include:

V600E—estimated to account for 80 percent of BRAF mutations.

V600K—estimated to account for most of the remaining BRAF mutations.

The FDA approved the BRAF inhibitor biological to treat the more common V600E mutation, and while it can be used to treat the V600K mutation, it is less effective and the treatment for this latter type of mutation considered an off-label use. It is critical to physicians and patients to know which BRAF mutation the patient has. However, the current FDA approved commercial kit for the BRAF mutation cannot distinguish between V600E and V600K. In contrast, the LDTs that physicians offer are designed to detect and distinguish the various mutations, making these tests more clinically relevant than the FDA commercial kit.

Testing for the BRAF mutation is an example of how pathologists, oncologists, medical geneticists, and other physicians engaged in laboratory medical practice are able to offer testing services to facilitate the rapid translation of new medical knowledge into clinical practice and provide patients access to the most up to date treatment options. Increasing the regulatory burden on laboratory medical practice will decrease patient access to most appropriate care and stifle the development of the next generation of tests that save lives and decrease health care costs through targeted and precision medical treatments.

Public Health Safety Network

Burdensome additional regulation of LDTs will slow the ability of physicians and clinical laboratories to develop tests to respond to infectious disease epidemics and bio-threats in the future. As one physician noted to the CLIA Advisory Board "...the ability of clinical laboratories to respond as they did [to the H1N1 epidemic] was very much tied to their ability to develop and validate their own assays, adhering to CLIA and CAP guidelines."¹

In April 2009, an unknown respiratory outbreak emerged in the U.S. and Mexico. The virus was identified as H1N1, which is a subtype of the Influenza A virus. The disease spread rapidly and there were over 2,000 cases reported by May. In June, the World Health Organization declared an H1N1 pandemic. By August 2010 when the pandemic was declared over, the novel H1N1 virus had spread to more than 214 countries and was the cause of death for over 18,000 people. A large number of CLIA regulated clinical laboratories employ physicians and other health care professionals who perform molecular testing for influenza on a routine basis. During the first week of the H1N1 outbreak, an

¹ Dr. Jan Nowak statement to CLIA Advisory Board, 2009.

informal survey of 43 laboratories by the Association of Molecular Pathology found that 40 of them had LDTs that could distinguish Influenza A from Influenza B and approximately 16 laboratories had LDTs that could identify H1N1 from other H1 viruses. Most results from these tests were available within 24 hours, speeding treatment of patients and decision-making by public health officials. Many of these laboratories were able to identify the existence and magnitude of the outbreak in advance of public health laboratories—in some cases many days in advance. The large network of physicians and other health care professionals in academic and community hospital laboratories throughout the U.S. who were able to develop and validate molecular tests in the first week of the outbreak to rule out H1N1 as the cause of a patient's illness played a critical role in controlling the H1N1 pandemic. The FDA did not have an approved commercial kit available for broad public use. It is essential to emphasize that efforts to shrink the number of laboratories or even to prevent physicians from offering such tests when competing FDA commercial kits exist degrades the capability of the nation's physicians and clinical laboratories to address the ever growing public health danger presented by the outbreak of infectious diseases and bio-threat. Creating legislative or regulatory exceptions for LDTs fails to account for the skill and expertise and experienced required to develop and validate such tests.

Current LDT Oversight and Regulation

Clinical laboratories have been subject to extensive federal and to lesser extent, except in New York, state laws and peer review "deemed" authorities. Presently, commercialized test kits that are manufactured and shipped to laboratories are regulated by the FDA, and testing services offered by physicians fall under the purview of laboratories, which are subject to CLIA oversight. Most testing in the U.S. is subject to the oversight of the College of American Pathologist (CAP) accreditation program, the State of New York program, or another accreditation program, which by law have the authority to deem laboratories compliant with CLIA. Both New York State and the CAP require that laboratories demonstrate the clinical validity of tests they offer and both demand considerably more from laboratories than CLIA requires.

AMA's Framework for Oversight

Assuring the quality of laboratory tests is important in delivering optimal care to patients. Accordingly, the AMA supports an oversight framework for LDTs including tests for genetic and acquired mutations that will ensure accuracy, reliability, and validity. An oversight framework should recognize the importance of the physician's role in the practice of medicine, and should not unduly restrict access to tests that physicians deem necessary and appropriate in the care of their patients.

The AMA supports a tiered, risk-based approach that confers assurance of analytic and clinical validity for all LDTs including genetic tests, but this does not mean such a framework serves as an endorsement of FDA oversight and regulation. Rather, the AMA would strongly support efforts to modernize the CLIA oversight infrastructure and enhance CLIA authorities. Risk should be determined by the potential for a misinterpreted result to cause harm to patient, and by test characteristics, e.g., test methodology that is not transparent nor well understood (as in the case of tests that use complex algorithms to produce results) would be in highest risk category. Any new oversight measures must be developed in collaboration with physicians and other health care providers who have

experience in accreditation and proficiency testing for laboratories conducting genetic tests, such as CAP and ACMG, for example. The oversight must preserve the clinical discretion of physician to choose test that he/she determines is appropriate for the clinical situation, whether or not it is a LDT or is FDA approved/ cleared. Furthermore, the labeling of drugs or biologicals for which tests inform indication and dosage decisions should not include the brand name of the test, nor make stipulations that the drug can only be prescribed with the prior use of an FDA-approved/cleared test.

The FDA Notice and Proposed Guidance Documents

The AMA has two broad legal concerns and a host of specific substantive clinical questions about the proposed guidance that we look forward to discussing with the agency. First, however, the AMA strongly urges this Subcommittee to consider the compelling need to avoid duplicative and confusing regulation by two federal agencies, a number of states, and accreditation bodies with deeming authority. The FDA has proposed a framework for regulation of LDTs, but has not clarified or coordinated with CMS, which is charged with administering CLIA compliance.

Just as Congress charged the FDA, the Federal Communications Commission, and the U.S. Department of Health & Human Services Office of the National Coordinator for Health Information Technology to develop a proposed regulatory framework for digital health to avoid duplicative and burdensome regulation, there is similarly an urgent need to, at a minimum, require CMS and the FDA to engage major stakeholders in a similarly transparent process and propose a framework that clearly and specificity identifies areas where the agencies will avoid duplicative, contradictory, and ambiguous oversight.

First, the AMA questions the FDA's legal standing to regulate LDTs. LDTs are not medical devices as defined in the Food, Drug, and Cosmetics Act (FDCA). LDTs are procedures for performing a test using inputs—reagents and laboratory equipment (which are regulated by the FDA). LDTs represent the technical expertise and clinical judgment of the physician who developed and validated the test. As a result, a LDT cannot be shipped to another laboratory nor are they manufactured. LDTs are procedures performed in a single laboratory and physicians continue to be legally responsible and accountable for LDTs.

Second, even assuming that the agency does have statutory authority, the agency in the past, through regulation finalized after notice and comment expressly limited the scope of its LDT regulation. As a result, the agency is precluded by well-established administrative law principles from imposing new and significant substantive changes through guidance documents. This is all the more important as the physicians, other health care professionals, and laboratories that the agency proposes to regulate are not manufacturers; therefore, there are a number of requirements that apply to medical devices—that do not have an obvious application to laboratory medical practice. If the agency does proceed with the current draft proposal, the AMA intends to strongly urge the agency to issue the new requirement through notice and comment. It is essential that an economic impact analysis is completed and analysis released outlining the anticipated impact of the new regulatory burdens on impacted stakeholders. Furthermore, given the large number of LDTs and the exceedingly small number of commercial kits that the FDA has approved/cleared, the AMA also would strongly urge the FDA and Congress to consider whether the agency has the requisite capacity to regulate in this space. The FDA has assumed a number of substantial new

regulatory authorities and has rapidly grown over a very short period of time in the past several years. There is a real danger that the relatively small number of existing FDA staff charged with oversight of commercial kits will not be adequate and scaling capacity with qualified and experienced individuals difficult given the expertise required.

On the substantive, front, the proposed framework provides that enforcement authority will be exercised for LDTs for rare diseases, “traditional” LDTs offered by a health care facility for a patient who is being diagnosed and/or treated at the same health care facility or the health system, and LDTs offered where no FDA approved or cleared commercial kit exists. We support the foregoing carve outs broadly speaking. However, the FDA’s proposed limitations of these carve outs are extreme and inadequate. The AMA also finds the FDA’s proposed treatment of LDTs where FDA commercial kit has been approved, troubling and contrary to efforts to innovate and provide the most appropriate medical care as demonstrated by the BRAF example provided above. Finally, the FDA’s proposed listing requirements for LDTs will represent a major regulatory and cost burden for physicians and laboratories. The list of information required is quite long, requiring every physician and laboratory in the United States to complete notification for every test they perform, even if those tests that qualify under one of the carve-outs.

We appreciate the Subcommittee’s critical role in advancing policies that accelerate and support the development and application of 21st Century tests and treatments into clinical practice and look forward to working with the Health Subcommittee, Congress, patients, regulators, and insurers to realize the promise of personalized medicine.

CLIA Overview...**What is CMS' authority regarding Laboratory Developed Tests (LDTs) and how does it differ from FDA's authority?**

The Clinical Laboratory Improvement Amendments (CLIA) program regulates laboratories that perform testing on patient specimens in order to ensure accurate and reliable test results. The FDA regulates manufacturers and devices under the Federal Food, Drug, and Cosmetic Act (FFDCA) to ensure that devices, including those intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, are reasonably safe and effective.

The FDA defines a Laboratory Developed Test (LDT) as an *in vitro* diagnostic test that is manufactured by and used within a single laboratory (i.e. a laboratory with a single CLIA certificate). LDTs are also sometimes called in-house developed tests, or "home brew" tests. Similar to other *in vitro* diagnostic tests, LDTs are considered "devices," as defined by the FFDCA, and are therefore subject to regulatory oversight by FDA.

When a laboratory develops a test system such as an LDT in-house without receiving FDA clearance or approval, CLIA prohibits the release of any test results prior to the laboratory establishing certain performance characteristics relating to analytical validity for the use of that test system in the laboratory's own environment, see 42 CFR 493.1253(b)(2) (establishment of performance specifications). This analytical validation is limited, however, to the specific conditions, staff, equipment and patient population of the particular laboratory, so the findings of these laboratory-specific analytical validation are not meaningful outside of the laboratory that did the analysis. Furthermore, the laboratory's analytical validation of LDTs is reviewed during its routine biennial survey – after the laboratory has already started testing.

In contrast, the FDA's review of analytical validity is done prior to the marketing of the test system, and therefore, prior to the use of the test system on patient specimens in the clinical diagnosis/treatment context. Moreover, the FDA's premarket clearance and approval processes assess the analytical validity of a test system in greater depth and scope. The FDA's processes also assess clinical validity, which is the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient, as part of the review that is focused on the safety and effectiveness of the test system. Furthermore, unlike the FDA regulatory scheme, CMS' CLIA program does not address the clinical validity of any test.

Thus, the two agencies' regulatory schemes are different in focus, scope and purpose, but they are intended to be complementary.

**Laboratory Developed Tests (LDTs)
Frequently Asked Questions**

1. What is a Laboratory Developed Test?

The FDA defines a Laboratory Developed Test (LDT) as an *in vitro* diagnostic test that is manufactured by and used within a single laboratory (i.e. a laboratory with a single CLIA certificate). LDTs are also referred to as in-house developed tests or “home brew” tests.

2. What is the difference between the CMS’ authority versus FDA’s authority regarding LDTs?

The Clinical Laboratory Improvement Amendments (CLIA) program regulates laboratories to ensure accurate and reliable test results when laboratories perform testing on patient specimens. The FDA regulates manufacturers and devices under the Federal Food, Drug, and Cosmetic Act (FFDCA) to ensure that devices, including those intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, are reasonably safe and effective.

Similar to other *in vitro* diagnostic tests, LDTs are considered “devices,” as defined by the FFDCA, and are therefore subject to regulatory oversight by FDA. Although the FFDCA requires manufacturers of all *in vitro* diagnostic devices (IVDs), including LDTs, to comply with the regulatory requirements governing device safety and effectiveness (such as quality controls for device design and other aspects of device manufacturing, premarket clearance/approval, etc.), the FDA has generally exercised enforcement discretion so that the agency has generally not enforced these requirements for LDTs. LDTs, therefore, generally have not undergone FDA premarket review, which assures both the analytical validity (e.g. analytical specificity and sensitivity, accuracy and precision) and clinical validity of IVDs.

Under the CLIA regulations, when a laboratory uses a test system that has not received FDA clearance or approval, such as a LDT, the laboratory may not release any test results prior to establishing certain performance characteristics relating to analytical validity for the use of that test system in the laboratory’s own environment, *see* 42 CFR 493.1253(b)(2) (establishment of performance specifications). CLIA and its implementing regulations do not affect FDA’s authority under the FDCA to regulate LDTs or other devices used by laboratories.

Further, CMS’ CLIA program does not address the clinical validity of any test – that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. On the other hand, FDA evaluates the clinical validity of a test under its premarket clearance and approval processes and as a result, has expertise in this area. In other words, the FDCA encompasses clinical validity whereas CLIA does not.

Thus, the regulatory schemes of the two agencies are different in focus, scope and purpose, but the two schemes are intended to be complementary.

3. What does CMS CLIA require for analytical validity for LDTs?

The analytical validation under CLIA looks at the performance characteristics of a test used to describe the quality of patient test results, and includes an analysis of accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference interval, and any other performance characteristics required for the test system in the laboratory that intends to use it. This analytical validation is limited to the specific conditions, staff, equipment and patient population of the particular laboratory, so the findings of these laboratory-specific analytical validation are not meaningful outside of the laboratory that did the analysis.

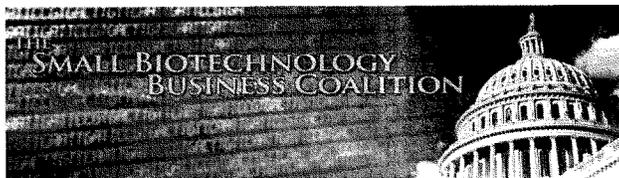
4. What is the difference between the CMS' analytical validity review versus the FDA's analytical validity review for LDTs?

The CMS' analytical validity review is intended to determine if a specific test finds what it is supposed to find (i.e. the analyte it is intended to detect) when laboratories perform testing on patient specimens. Therefore, the analytical validation must be performed by the laboratory intending to use the test on patient specimens. Furthermore, the laboratory's analytical validation of a LDT is reviewed during its routine biennial survey – after the laboratory has already started testing. Moreover, the routine CLIA survey does not include a review of the clinical validation of a LDT – that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient.

In contrast, the FDA's review of analytical validity is done prior to the marketing of the test system, and therefore, prior to the use of the test system on patient specimens in the clinical diagnosis/treatment context. Further, the FDA's analytical validity review is more in-depth and more comprehensive than that of the CLIA program, and it is focused on the test system's safety and effectiveness. As a result, FDA review may uncover errors in test design or other problems with a test system. Also, while CMS' CLIA program does not address the clinical validity of any test, FDA's premarket review of a test system includes an assessment of clinical validity.

5. What does CMS CLIA require for laboratories performing LDTs?

The CLIA requirements are based on the test complexity; the more complex the test is to perform, the more stringent the requirements. LDTs are considered high complexity tests. Therefore, the laboratory must meet all applicable CLIA requirements for high complexity testing.



Comments of Small Biotechnology Business Coalition¹

For the September 9, 2014

House Energy & Commerce Committee Hearing:

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

Small biotechnology companies are the primary developers of innovative diagnostic tests that address unmet medical needs. We estimate that there are over 800 small companies in the U.S. developing and validating tests to aid in earlier and more definitive diagnosis and in therapeutic decision making.

On July 31, 2014, the Food and Drug Administration (FDA) notified Congress that it intends to issue Draft Guidance to regulate Laboratory Developed Tests (LDTs). A widespread concern among small diagnostics companies is that the high costs of compliance with these anticipated regulations in the face of unpredictable commercial returns would prevent them from attracting the capital needed to bring their products to market. Our companies already face general disinterest from the venture capital community as a result of very low reimbursement rates for diagnostic test coupled with the difficulty of obtaining patent protection for novel biomarkers or test as a result of two recent U.S. Supreme Decisions that considerably narrowed patent protection for this subject matter.²

FDA regulation of LDTs should not be permitted to progress unless exemptions are provided for small companies developing innovative tests that address unmet medical needs. Our organization is proposing a new regulatory mechanism for simultaneously encouraging innovation while at the same time protecting patients and delivering tests that can substantially improve disease outcomes. This concept is modeled after the FDA's Small Business Nutrition Labelling Exemption and the Humanitarian Device Exemption

¹ www.SmallBiotechCoalition.org The SBBC was founded in February 2010 to promote government policies that aid the estimated 2000+ independently owned, privately held small biotech companies. The vast majority of these companies are financed through the SBIR program and individual ("Angel") investors rather than VCs.

² [Myriad v. AMP](#) and [Mayo v. Prometheus](#)

The proposed exemption would apply to innovative tests developed by small businesses that would otherwise be deemed to be Class III diagnostics (most complex, high risk and novel intended uses) requiring premarket approval (PMA). These diagnostics—to be known as —“Small Business Developed Innovative Tests” or —“SBDIT”s—could instead be subject to a new —“provisional PMA” that would permit marketing and administration of the test to up to 8,000 U.S. patients per year or \$8 million in annual revenue.

An application for a small business provisional PMA would be similar in both form and content to a regular PMA application, but without the same amount of clinical trial data typically required for PMAs. FDA could reject only those applications that pose an unreasonable or significant risk to patients, and where the likely benefit to health is clearly outweighed by the risks, taking into account the probable risks and benefits of currently available devices or alternative testing paradigms. Additionally, the applicant must demonstrate that no comparable tests are on the market, and that they could not otherwise bear the cost of a traditional PMA. In this regard the standard would be very similar to that of a Humanitarian Device Exemption (HDE).

This exemption would help break the “Catch-22” facing most innovative small diagnostics companies who face the challenge of accessing capital to fund expensive clinical studies without conclusive evidence that their test will gain regulatory approval and marketplace acceptance.

Data derived from the first few years of marketing could be collected and analyzed becoming the equivalent of a large scale, prospective clinical study that would otherwise be prohibitively expensive for small companies. During this provisional period companies could ascertain market demand for their test and in some cases obtain reimbursement from CMS and/or private payers. This would significantly decrease uncertainty for investors permitting the company to more readily obtain funding for more research and development and product improvements.

The Humanitarian Device Exemption (HDE) was established based on the recognition that companies’ research and development costs typically exceed their market returns for devices and diagnostics addressing small patient populations (under 4,000 U.S. patients per year). HDEs provide an incentive for the development of products for these diseases by eliminating the requirement of proving efficacy. The economic rationale for HDEs also supports similar incentives for small business notwithstanding the fact that the later ultimately may address substantially larger markets. Investigational Device Exemptions (IDEs) are designed for devices and diagnostics for which effectiveness data is being gathered prior to marketing. The proposed small business exception also permits the gathering of this data but in the context of a limited initial marketing campaign to early adopters.

For further information please contact

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United States House of Representatives
Committee on Energy and Commerce, Subcommittee on Health

Hearing on

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

Written testimony submitted by
Association for Molecular Pathology

September 9, 2014

Dear Chairman Pitts and Ranking Member Pallone,

Thank you for the opportunity to submit written testimony for the hearing titled, "21st Century Cures: Examining the Regulation of Laboratory Developed Tests." The Association for Molecular Pathology (AMP) is an international medical 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 and commercial clinical laboratories, community hospitals, and the *in vitro* diagnostics industry.

AMP has been an active participant in the ongoing discussion among policymakers and other stakeholders on the oversight and regulation of laboratory developed tests (LDTs). The Association has provided public comments to the Food and Drug Administration (FDA) many times over the past ten years and in January 2014, AMP published a revised position statement on the oversight and regulation of molecular-based LDTs.¹ We encourage the Committee to review this new position statement as it considers policy on the issue. We are very pleased that you are holding a hearing on this important topic today.

The FDA's Notification to Congress to establish a framework to regulate LDTs is a very dramatic shift from the Agency's current position of enforcement discretion. It is an historic break from the traditional regulation of clinical laboratories, the basis for which has been the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and state level requirements. We believe the FDA's proposal to regulate clinical laboratories is unjustified and will be detrimental to both patients and providers. As such, the FDA should engage in a very transparent and open process of formal rulemaking, with multiple opportunities to provide public comment prior to embarking on this course. Additionally, we believe FDA's proposed framework would impose a substantial economic burden on clinical laboratories that would potentially threaten patient access to important medical services. Therefore, we strongly encourage Congress to require the agency to complete an economic impact study of the framework prior to FDA's finalizing and implementing its requirements. Upon initial review of the details in the Notification, AMP has numerous specific concerns with the proposed framework as well as many clarifying questions. The Association will continue to analyze the framework and intends to submit comments during the public comment period once the guidance document is officially noticed in the Federal Register.

In the interim, AMP appreciates the opportunity to provide this written testimony on the regulation of LDTs and offers its assistance and expertise to you, your colleagues, and your staff as you consider this issue and continue your work on the Path to 21st Century Cures.

¹ <http://imd.ampathol.org/article/51525-1578/13j00221-3/pdf>

Laboratory Developed Procedures:

AMP members are not manufacturers, but rather health care providers who provide laboratory services to our patients. We are physicians and board-certified doctoral level scientists, who have extensive education and training in our fields. Molecular pathology professionals design tests after assessing that they will be medically useful and they do so often at the request of oncologists, pediatricians and other physicians who need the information to help guide their patient management decisions. The stringent validation process includes establishing both analytic and clinical validity. In addition, molecular pathology professionals consult with ordering physicians in determining the appropriate tests to perform, given an individual patient's clinical presentation. We then interpret the results of the testing in the context of other medical information. These factors distinguish LDTs from medical devices, such as artificial joints or *in vitro* diagnostic test kits that are sold and distributed to laboratories around the world. AMP believes that any changes in the oversight of clinical laboratories should acknowledge these differences.

To clearly distinguish LDTs from traditional medical devices, AMP proposes referring to these tests 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. The term LDP better represents the nature of complex laboratory testing, which is very much a medical service provided by appropriately trained and qualified professionals.

Regulation of LDPs:

For the vast majority of LDPs, AMP believes that the CLIA program at the CMS is the appropriate vehicle through which to conduct oversight. CLIA requires laboratories to establish for each test system the performance specifications for accuracy, precision, analytical sensitivity, analytical specificity, reportable range of test results, reference intervals, and other performance requirements. We believe the requirements the CLIA regulations impose on laboratory directors and mandated clinical consultants, as well as the expertise of ordering physicians, address the need to ensure the clinical validity of tests that laboratories provide. However, any perceived gaps in such regulations could be straightforwardly addressed by simply modifying these regulations. Further CMS can increase transparency in its regulatory process for the public, by updating its information technology infrastructure to make CLIA's registry of laboratories and their test offerings easily and readily available online.

Thank you again for the opportunity to provide testimony to your hearing on the regulation of LDPs. As health care professionals, patient care is our highest priority. The current regulatory framework has worked well for the vast majority of laboratory tests and has provided laboratories with the flexibility to develop new assays, adapt FDA cleared assays to specific circumstances, rapidly and continually improve and upgrade the quality of tests in response to increased medical knowledge. LDPs have made important contributions to patient care, and have played a key role in advancing diagnostics generally. The imposition of an extensive new regulatory scheme such as that proposed by FDA poses an enormous threat to future diagnostic development, and to the health and well-being of our patients.

We hope that the information provided helps inform your work and please do not hesitate to contact AMP's Executive Director, Mary Williams, at mwilliams@amp.org if we may be of assistance.



United States House of Representatives
Committee on Energy and Commerce, Subcommittee on Health

Hearing on

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

Written testimony submitted by
Invitae Corporation

September 9, 2014

Chairman Pitts and Ranking Member Pallone,

Thank you for the opportunity to submit written testimony for the hearing titled, “21st Century Cures: Examining the Regulation of Laboratory Developed Tests.” Founded in 2012, Invitae is a genetic information company whose mission is to bring comprehensive genetic information into routine medical practice to improve the quality of healthcare for billions of people. Specializing in genetic diagnostics for hereditary disorders, Invitae is aggregating the world’s genetic tests into a single service with better quality, faster turnaround time, and a lower price than most single-gene diagnostic tests today.

Invitae currently operates a CLIA-certified laboratory in San Francisco, California, from which we offer tests for over 200 hereditary conditions using a single assay for a price of \$1500, regardless of the test ordered. As required by CLIA, all of our testing services are physician-mediated; only licensed medical professionals can order tests from Invitae. Since the launch of our service in late 2013, we have seen rapid growth in testing volume, which indicates to us that there is an unmet need for high quality, low cost genetic testing services with enhanced customer service.

As you undoubtedly know, policy discussions on whether or not to modify the United States Food and Drug Administration’s (FDA) position of enforcement discretion for laboratory developed tests (LDTs) have been occurring for more than a decade now. Invitae is generally supportive of a regulatory approach that provides medical professionals and their patients with confidence in the quality of the testing services they receive, without unduly interfering with rapid progress in a dynamic area of the health care system that has the promise of delivering better care to patients while reducing overall healthcare costs.

Since the FDA’s announcement of its intention to publish guidance documents establishing a framework to regulate LDTs in 2010, stakeholders from numerous perspectives including patients, providers, clinical laboratories, and diagnostic companies have called for clarity in the review requirements and regulatory pathways that may be applied to some categories of LDTs. Given the significance of the change in regulatory policy detailed in the Notification to Congress, Invitae plans to submit comments during the public comment period and at the anticipated public meeting. In the interim, we greatly appreciate the Committee focusing its attention on this very

important issue and we hope our comments help inform your discussion as you consider FDA regulation of LDTs and policy opportunities to advance the Path to 21st Century Cures initiative.

In several respects the FDA's draft guidance takes into account industry feedback from prior discussions. While the FDA believed the framework described in its Notification to Congress and the soon to be published draft guidance documents would indeed provide clarity, in fact it raises many questions and poses some risks that could have a profound impact on Invitae's ability to improve its tests so that patients have access to the highest quality and most up to date testing services. For that reason, as the Committee continues its work on the Path to 21st Century Cures initiative and explore the complicated issue of regulation of LDTs, we encourage you to consider the following areas that require additional clarification.

Clarifying the definition of a LDT:

The definition of LDT included in the FDA's notification to Congress remains unclear. Several ambiguities could create particular problems for Invitae and other labs providing tests for hereditary conditions.

For example, the draft guidance seems to imply that a testing service is not an LDT if the provider operates more than one facility from which it delivers the test. It is unclear how such a service would be regulated as soon as the operator opens a second laboratory. Given the early demand that Invitae has seen for its testing services, we certainly anticipate the need for a second lab in the not-too-distant future. We currently have a mirror CLIA-certified lab in Santiago, Chile, which we expect will address some of the international demand for our services. It would certainly be unfortunate if FDA regulation limited Invitae's ability to deliver tests to US patients, with the result that patients in foreign countries would have greater access to new tests than those in the United States.

As this is a central component underlying the regulatory framework, FDA needs to provide further explanation as to what tests the agency considers to be LDTs that would be subject to the proposed regulatory framework.

Documenting clinical validity:

Clinical laboratories utilize a variety of data, tools, and resources to develop and validate their tests. While the ideal trial design for drug approvals is randomized controlled trials, for the majority of diagnostics, this is unnecessary due to the availability of information already in existence. According to the National Institutes of Health (NIH) Genetics Home Reference, clinical validity refers to how well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease. The Human Genome Project, subsequent research publications, NIH biomarker databases, and more have provided an abundance of peer reviewed literature, coalesced information, and other resources to establish the clinical validity of genetic variants.

The Notification to Congress does state that the FDA expects that for many LDTs, clinical validity has already been established in the literature. However, it does not provide clear guidance that a review of retrospective data in lieu of a randomized controlled trial is sufficient and an acceptable manner to evaluate clinical validity in moderate risk LDTs. In the case of hereditary

conditions, there is a great deal of literature documenting the role of particular genes, and the impact of genetic variations in those genes, on particular diseases. At the same time, novel variants in those genes are identified all the time. At Invitae, the determination that a novel variant is likely pathological, likely benign, or has unknown significance, involves the judgment and analysis of highly trained genetic experts.

A participant in the Free the Data initiative, Invitae shares anonymized versions of these conclusions, along with their bases, with publicly-available databases such as ClinVar, operated by the NIH, so that clinicians and researchers can provide peer review and benefit from Invitae's experience. If the proposed FDA regulations limited Invitae's services not only to genes whose relations to hereditary diseases have been validated, but also to specific variants, this medical progress would be significantly impeded, as would the comprehensiveness of the results provided to individual patients.

Maintaining the ability to modify and improve LDTs already cleared or approved:

The scientific understanding of genomics is continuously growing and as such, molecular diagnostics are often updated to improve the test's sensitivity or to reduce costs and expense to the healthcare system. Often times, a LDT will be modified for use in a different sample type such as blood or saliva. However, these changes do not affect the tests' clinical validity and their relevance to clinical decision making. If a modification is made to an already FDA cleared or approved LDT, the draft guidance says that these modified tests must be subject to a subsequent premarket review. This would be a very burdensome process to complete each and every time a modification to a LDT is warranted and in the end, would only delay innovation, eliminate any motivation to continuously update and improve a test, and ultimately create barriers to patients' access to the latest advances in molecular diagnostics. The current CLIA standards, if appropriately enforced, should provide adequate assurance as to the validity and reproducibility of tests incorporating these modifications without requiring pre-market approval every time a laboratory implements a process improvement. Some of the hallmarks of laboratory medicine are its ability to be nimble, quickly develop tests for emerging diseases, and bring the latest technology to the clinic. The FDA should promote policy that supports the laboratory's ability to be nimble and modify tests as needed.

Thank you again for the opportunity to submit this written testimony for your hearing on the regulation of LDTs. Please do not hesitate to contact me by phone (650-823-3949) or by email (randy.scott@invitae.com), if we may be of assistance in the future or if you have any questions about our testimony.

Sincerely,



Randy Scott
Chairman and CEO
Invitae Corporation
458 Brannan Street
San Francisco, CA 94107
<https://www.invitae.com>



September 9, 2014

The Honorable Joseph Pitts
Chairman
House Energy and Commerce Subcommittee on Health
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Frank Pallone
Ranking Member
House Energy and Commerce Subcommittee on Health
U.S. House of Representatives
2415 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Pitts and Ranking Member Pallone:

On behalf of the American Association of Bioanalysts (AAB) and the National Independent Laboratory Association (NILA), representing independent community and regional clinical laboratories, we thank you for holding today's hearing, "21st Century Cures: Examining the Regulation of Laboratory Developed Tests."

AAB administers one of the nation's largest full-service proficiency testing programs approved by the Clinical Laboratory Improvement Amendments of 1988 (CLIA), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), Centers for Medicaid and Medicare Service (CMS), and all state agencies to satisfy laboratory proficiency testing requirements. NILA's members are community-based laboratories that range in size from intra-state to multi-state regional community laboratories. In addition to providing diagnostic laboratory services relied on by physicians across the country every day, a number of AAB and NILA members are engaged in the development of laboratory tests that provide patients and their physicians access to safe and effective testing options.

Laboratory Developed Tests (LDTs) offer patients the potential to prevent disease, obtain early diagnoses, and receive the most accurate and best course of treatment from their health care provider. Any regulatory process to oversee LDTs must incorporate the promise these tests hold without stifling innovation, while simultaneously ensuring that patient safety remains paramount. Physicians must be able to rely on and trust the results provided from an LDT to make the best clinical decisions for patients.

American Association of Bioanalysts/National Independent Laboratory Association
Subcommittee Hearing:
21st Century Cures: Examining the Regulation of Laboratory Developed Tests
September 9, 2014

Page 2

As health care providers and as providers of federal and state approved proficiency testing, AAB and NILA strongly believe that LDT technology must be accurate, reliable and reproducible, and that the primary goal of regulatory oversight of LDTs should be to avoid potentially life-altering or life-threatening implications from an inaccurate or misleading test result.

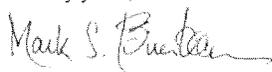
Since 1988, the clinical laboratory industry has been regulated through CLIA (P.L. 100-578) by CMS, an agency program that understands and has direct experience with laboratory testing. Additional oversight of laboratory testing is provided by the College of American Pathologists, the Joint Commission on Accreditation of Healthcare Organizations, and other accrediting organizations "deemed" by the government to provide such oversight.

The current CLIA regulatory framework was designed over 22 years ago. Dramatic changes in clinical laboratory testing have occurred since then and will continue to occur at a rapid pace. As a result, elements of CLIA's regulatory framework need to be updated and modernized to better address LDTs and emerging disciplines such as genomics, proteomics, and pharmacogenetics. We believe Congress should ensure that CLIA has the resources, technical expertise, and flexibility to provide, enforce, and maintain a 21st Century regulatory system for LDTs and other emerging disciplines.

AAB and NILA are committed to working with the Committee, the federal agencies, and the patient community to address these challenges. It is important that we collaborate to ensure that a fair and sustainable regulatory process is in place to assess the quality and safety of LDTs while allowing for continued innovation.

Thank you again for today's subcommittee hearing on this important issue. We applaud the Committee's focus and work on the 21st Century Cures Initiative. Clinical laboratories should be viewed as a central partner in advancing clinical care and reducing health care costs. We look forward to continuing to work with you. Should you have any questions, or require additional information, please contact Julie Scott Allen, our Washington representative, at (202) 230-5126 or julie.allen@dbr.com.

Sincerely yours,



Mark S. Birenbaum, Ph.D.
Administrator

cc: Committee Members

The Honorable Joe Pitts and Frank Pallone, Jr.
Page 2 of 2

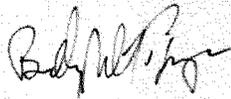
Through the 21st Century Cures Initiative, Congress could facilitate the regulatory policy process through legislation that requires relevant federal agencies (e.g., FDA and CMS), and other stakeholders, to work together to develop a final regulatory framework within a reasonable timetable. More specifically,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

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

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

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

Sincerely,



Bradley Merrill Thompson
On Behalf of the Combination Products Coalition

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July 7, 2011

How Bright Promise in Cancer Testing Fell Apart

By GINA KOLATA

When Juliet Jacobs found out she had lung cancer, she was terrified, but realized that her hope lay in getting the best treatment medicine could offer. So she got a second opinion, then a third. In February of 2010, she ended up at Duke University, where she entered a research study whose promise seemed stunning.

Doctors would assess her tumor cells, looking for gene patterns that would determine which drugs would best attack her particular cancer. She would not waste precious time with ineffective drugs or trial-and-error treatment. The Duke program — considered a breakthrough at the time — was the first fruit of the new genomics, a way of letting a cancer cell's own genes reveal the cancer's weaknesses.

But the research at Duke turned out to be wrong. Its gene-based tests proved worthless, and the research behind them was discredited. Ms. Jacobs died a few months after treatment, and her husband and other patients' relatives have retained lawyers.

The episode is a stark illustration of serious problems in a field in which the medical community has placed great hope: using patterns from large groups of genes or other molecules to improve the detection and treatment of cancer. Companies have been formed and products have been introduced that claim to use genetics in this way, but assertions have turned out to be unfounded. While researchers agree there is great promise in this science, it has yet to yield many reliable methods for diagnosing cancer or identifying the best treatment.

Instead, as patients and their doctors try to make critical decisions about serious illnesses, they may be getting worthless information that is based on bad science. The scientific world is concerned enough that two prominent groups, the National Cancer Institute and the Institute of Medicine, have begun examining the Duke case; they hope to find new ways to evaluate claims based on emerging and complex analyses of patterns of genes and other molecules.

So far, the Food and Drug Administration "has generally not enforced" its regulation of tests created by individual labs because, until recently, such tests were relatively simple and relied

heavily on the expertise of a particular doctor, said Erica Jefferson, a spokeswoman for the agency. But now, with labs offering more complex tests on a large scale, the F.D.A. is taking a new look at enforcement.

Dr. Scott Ramsey, director of cancer outcomes research at the Fred Hutchinson Cancer Center in Seattle, says there is already “a mini-gold rush” of companies trying to market tests based on the new techniques, at a time when good science has not caught up with the financial push. “That’s the scariest part of all,” Dr. Ramsey said.

Doctors say the heart of the problem is the intricacy of the analyses in this emerging field and the difficulty in finding errors. Even well-respected scientists often “oversee a machine they do not understand and cannot supervise directly” because each segment of the research requires different areas of expertise, said Dr. Lajos Pusztai, a breast cancer researcher at M. D. Anderson Cancer Center at the University of Texas. As a senior scientist, he added, “It’s true for me, too.”

The Duke case came right after two other claims that gave medical researchers pause. Like the Duke case, they used complex analyses to detect patterns of genes or cell proteins. But these were tests that were supposed to find ovarian cancer in patients’ blood. One, OvaSure, was developed by a Yale scientist, Dr. Gil G. Mor, licensed by the university and sold to patients before it was found to be useless.

The other, OvaCheck, was developed by a company, Correlogic, with contributions from scientists from the National Cancer Institute and the Food and Drug Administration. Major commercial labs licensed it and were about to start using it before two statisticians from M. D. Anderson discovered and publicized its faults.

The Duke saga began when a prestigious journal, Nature Medicine, published a paper on Nov. 6, 2006, by Dr. Anil Potti, a cancer researcher at Duke University Medical Center; Joseph R. Nevins, a senior scientist there; and their colleagues. They wrote about genomic tests they developed that looked at the molecular traits of a cancerous tumor and figured out which chemotherapy would work best.

Other groups of cancer researchers had been trying to do the same thing.

“Our group was despondent to get beaten out,” said Dr. John Minna, a lung cancer researcher at the University of Texas Southwestern Medical Center. But Dr. Minna rallied; at the very least, he thought, he would make use of this incredible discovery to select drugs for lung cancer patients.

First, though, he asked two statisticians at M. D. Anderson, Keith Baggerly and Kevin

Coombes, to check the work. Several other doctors approached them with the same request.

Dr. Baggerly and Dr. Coombes found errors almost immediately. Some seemed careless — moving a row or a column over by one in a giant spreadsheet — while others seemed inexplicable. The Duke team shrugged them off as “clerical errors.”

And the Duke researchers continued to publish papers on their genomic signatures in prestigious journals. Meanwhile, they started three trials using the work to decide which drugs to give patients.

Dr. Baggerly and Dr. Coombes tried to sound an alarm. They got the attention of the National Cancer Institute, whose own investigators wanted to use the Duke system in a clinical trial but were dissuaded by the criticisms. Finally, they published their analysis in *The Annals of Applied Statistics*, a journal that medical scientists rarely read.

The situation finally grabbed the cancer world’s attention last July, not because of the efforts of Dr. Baggerly and Dr. Coombes, but because a trade publication, *The Cancer Letter*, reported that the lead researcher, Dr. Potti, had falsified parts of his résumé. He claimed, among other things, that he had been a Rhodes scholar.

“It took that to make people sit up and take notice,” said Dr. Steven Goodman, professor of oncology, pediatrics, epidemiology and biostatistics at Johns Hopkins University.

In the end, four gene signature papers were retracted. Duke shut down three trials using the results. Dr. Potti resigned from Duke. He declined to be interviewed for this article. His collaborator and mentor, Dr. Nevins, no longer directs one of Duke’s genomics centers.

The cancer world is reeling.

The Duke researchers had even set up a company — now disbanded — and planned to sell their test to determine cancer treatments. Duke cancer patients and their families, including Mrs. Jacobs’s husband, Walter Jacobs, say they feel angry and betrayed. And medical researchers see the story as a call to action. With such huge data sets and complicated analyses, researchers can no longer trust their hunches that a result does — or does not — make sense.

“Our intuition is pretty darn poor,” Dr. Baggerly said.

This article has been revised to reflect the following correction:

Correction: July 7, 2011

An earlier version of this article misstated Dr. Steven Goodman's affiliation at Johns Hopkins University. He is a professor of oncology, pediatrics, epidemiology and biostatistics, not the director of oncology biostatistics.

This article has been revised to reflect the following correction:

Correction: July 16, 2011

An article on July 8 about the promise and pitfalls of using genetics to detect and treat cancer overstated the legal action taken by relatives of patients who received treatment in a research study at Duke University. The relatives, including Walter Jacobs, whose wife died a few months after treatment, have retained lawyers, but they have not sued Duke.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Majority (202) 226-2827
Minority (202) 226-3541

September 30, 2014

Dr. Jeffrey E. Shuren
Director
Center for Device and Radiological Health
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Shuren:

Thank you for appearing before the Subcommittee on Health on Tuesday, September 9, 2014, to testify at the hearing entitled "21st Century Cures: Examining the Regulation of Laboratory Developed Tests."

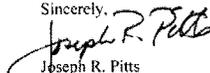
Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Wednesday, October 15, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to Sydne.Harwick@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,


Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Ministry (202) 225-2127
Ministry (202) 225-2641

September 30, 2014

Dr. Kathleen Behrens Wilsey
Co-Founder
KEW Group
840 Memorial Drive
Cambridge, MA 02139

Dear Dr. Behrens Wilsey:

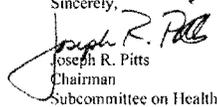
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Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,


Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment



October 3, 2014

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Dear Chairman Pitts:

I am pleased to respond to your request of September 30, 2014 regarding my testimony before the Subcommittee on Health on Tuesday, September 9, 2014 at the hearing entitled "21st Century Cures: Examining the Regulation of Laboratory Developed Tests." This letter provides my response to the additional question for the record from Dr. Burgess that I received:

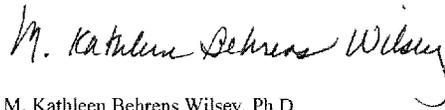
The Honorable Michael C. Burgess

- I. **The FDA has cleared a few LDTs with labeling statements that include limitations against use of the tests for treatment selection or even to make a diagnosis. With a manufacturer-distributed kit, a laboratory can use the kit "off label" in practice of laboratory medicine, without running afoul of FDA's promotional rules. With an LDT, however, if FDA considers the laboratory to be a "manufacturer" and considers the LDT service to be a "device" subject to FDA's labeling rules, this could raise concerns that the laboratory is "promoting" off-label use if it performs a test with labeling restricting the use for treatment or diagnostic purposes when the laboratory knows that the treating physician does not intend to use the test for such purposes. From your perspective as an investor in laboratories performing LDTs, how would this risk impact your decision to invest in these innovative companies?**

Thank you, Dr. Burgess, for raising this important issue. The Coalition for 21st Century Medicine identified this concern a number of years ago, and has raised this with FDA on a number of occasions. Laboratories have a longstanding practice whereby they provide consultation to treating physicians to help them understand how to use their tests in patient management, which is required under CLIA regulations. However, FDA labeling rules for devices restrict communication between manufacturers and physicians to prevent "promoting" off-label use. Unfortunately, we have not received any assurances that routine communications between laboratories and treating physicians would be protected from challenge as off-label promotion. In the absence of clear, written rules addressing this concern in a way that recognizes that laboratories are medical service providers

involved with provider-to-provider communications and that reconciles this conflict between CLIA regulations and FDA promotional rules, laboratories who offer LDTs will be at significant risk of potentially serious and onerous penalties. In my view, this risk would definitely chill investment in innovative biotechnology companies developing personalized diagnostics as LDTs.

Sincerely,

A handwritten signature in black ink that reads "M. Kathleen Behrens Wilsey". The signature is written in a cursive style with a large, looping initial "M".

M. Kathleen Behrens Wilsey, Ph.D.
Co-founder, Coalition for Twenty-first Century Medicine

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Majority (202): 225-2627
Minority (202): 225-3641

September 30, 2014

Mr. Alan Mertz
President
American Clinical Laboratory Association
1100 New York Avenue, N.W., Suite 725 West
Washington, D.C. 20005

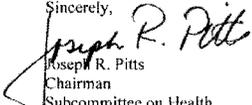
Dear Mr. Mertz:

Thank you for appearing before the Subcommittee on Health on Tuesday, September 9, 2014, to testify at the hearing entitled "21st Century Cures: Examining the Regulation of Laboratory Developed Tests."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, October 15, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to Sydne.Harwick@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

October 15, 2014

Sydne Harwick
Legislative Clerk
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515



Via USPS and Electronic Mail to: sydne.harwick@mail.house.gov

**RE: 21st Century Cures: Examining the Regulation of Laboratory Developed Tests -
Questions for the Record**

Dear Ms. Harwick,

Per your letter dated September 30, 2014, attached are my responses to the additional questions for the record brought forth by the Honorable Michael C. Burgess.

ACLA greatly appreciated the opportunity to participate in the September 9, 2014 21st Century Cures hearing, "Examining the Regulation of Laboratory Developed Tests". The 21st Century Cures Initiative hosted by Chairman Fred Upton and Rep. Diana DeGette has been a critical dialogue between Congress and health care stakeholders on ensuring medical innovation continues in the United States to improve the quality and access of care available to patients.

As has been mentioned in multiple Cures hearings and roundtables, clinical laboratory diagnostics, including molecular and genomic testing, play a crucial role in diagnosing and characterizing diseases so that patients can receive the best treatment sooner. Laboratory developed tests (LDTs) have been at the forefront of this innovation, lowering costs and saving lives. The FDA's proposal to newly apply the FDA medical device oversight framework to LDTs and laboratories threatens this innovation by duplicating costs and standards that already exist under the Clinical Laboratory Improvement Amendments and by creating new barriers to patient access.

ACLA looks forward to continuing work with the Committee to ensure robust innovation in clinical laboratory diagnostics that will lower health care costs and improve the quality of care available to patients.

Sincerely,

A handwritten signature in black ink that reads "Alan Mertz".

Alan Mertz
President
American Clinical Laboratory Association

The Honorable Michael C. Burgess

1. **Some advocates in favor of the FDA intervening in LDTs have suggested that laboratory tests are unregulated (or inadequately regulated) because they have not been required to go through FDA review. Is this the case? Have LDTs been unregulated all these decades that FDA claims to have been exercising “enforcement discretion?”**

No, this is not the case.

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. 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 are also subject to inspections under both CLIA and state law.

Further, moderate and highly complex laboratories, including all ACLA members, can 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.”

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 modifications would be so burdensome, the manufacturer has not modified the test to keep up to date with the medical science.” Advances such as these “came about because of, and would not have been possible without, the current regulatory framework governing LDTs.”

2. Reimbursement for most diagnostic tests is very low. If the anticipated revenue for a test over time is lower than what a company would need to spend for FDA pre-market approval will companies now abandon development of tests that can benefit our healthcare system?

Reimbursement for diagnostics has experienced extreme downward pressure in both the private and public payer settings over the last few years. Many laboratories, particularly those in the molecular and genetic testing space which has been so crucial to the personalized medicine revolution, have faced unsustainable reimbursement rates that in some cases do not cover the basic costs of performing the tests. Certainly layering additional burdensome and duplicative regulatory requirements on top of the existing oversight framework will dramatically increase the cost of development for any test, and will likely prevent laboratories from moving forward with many promising new tests for which they are already unlikely to recoup the cost of investment, even without the additional layer of regulation under the FDA.

Many tests today are available only as LDTs. The reasons vary. In some cases, there is no financial incentive to perform clinical trials and seek FDA approval or clearance of a test for a well-accepted, clinically recognized biomarker, because the test will serve only a small patient population. In other cases, a kit has not yet completed the FDA authorization process.

With evolving medical technology, clinical laboratories are well positioned to develop more novel LDTs that will diagnose or otherwise allow evaluation of other diseases and conditions for which there is no available IVD test kit. But if FDA moves forward in regulating this testing under its device authorities, many of the tests will become unavailable, with adverse effects on patient care. Some of these tests will never generate the financial returns needed to justify the costs of obtaining FDA clearance or approval, notwithstanding well-accepted and recognized clinical support in the form of peer-reviewed research and/or laboratory-based studies. Clinical laboratories currently are filling a significant gap for individuals with these diseases, and FDA regulation would preclude them from service these medical needs. Even if some laboratories elect to pursue the FDA authorization process rather than discontinuing their tests, they would need significant time to generate data needed to support a submission and to obtain approval of that submission. During this time, FDA regulation could preclude availability of these LDTs, which would compromise patient care.

3. How will the FDA proposed LDT regulations impact current CLIA certification process? Will it weaken CLIA or cause duplication, redundancy and excessive administrative burdens on small companies?

Presently, it is difficult to see how the FDA's proposed LDT regulations will impact the current CLIA certification process, as 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 (QSR), and yet there is no discussion of how the two separate regulatory authorities would regulate the laboratory industry in a way that would not impede innovation. The Agency, apparently acknowledging the very clear potential for overlapping and duplicative regulatory requirements, had discussed a third guidance document that it planned to release with the actual draft guidance which was to specifically address how the QSR requirements applicable to devices under the FDA would interplay with the quality requirements under CLIA. The Agency did not release such a document with the formal release of the Draft Guidance

documents, and has stated that it no longer plans to release such a guidance document. Rather, it has said that it will rely on a third-party organization to explain how CLIA and FDA's QSR requirements could be reconciled. ACLA believes that it is wholly inappropriate for FDA to leave such a vital issue to an unaccountable third party to resolve.

Laboratories would bear substantial burdens in seeking to comply with FDA requirements applicable to devices, even if only a subset of LDTs were determined to be subject to premarket review. Laboratories likely would need to adopt wholly new procedures and processes to comply with FDA's QSR requirements, which would pose special challenges because FDA has not defined how QSR requirements would apply in the laboratory context. Laboratories also would need to comply with adverse event reporting, labeling, and promotional requirements. These requirements would apply even if FDA regulated only one of a laboratory's LDTs. Laboratories also would be likely to encounter challenges in complying with both CLIA and the FDCA. For example, it could be difficult to comply with FDA promotional requirements while fulfilling CLIA requirements to offer consultation on interpreting test results. And although CLIA regulations require laboratories to provide pertinent updates on testing information as soon as it is available, FDA requirements for obtaining approval or clearance of labeling changes could preclude this action. Laboratories also would encounter duplicative regulation, such as inspection by both FDA and CMS. This additional regulatory burden would be both costly and unwarranted, and particularly onerous for smaller laboratories.