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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, D.C.

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).

This is a preliminary, unedited transcript. The statements within may be inaccurate, incomplete, or misattributed to the speaker. A link to the final, official transcript will be posted on the Committee's website as soon as it is available.

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.

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 Primarily focuses on FDA's July 31, 2014, notification to Congress that it intends to issue draft guidance on a framework for oversight of the laboratory developed test, the LDTs.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It is indisputable that the draft guidance documents the Agency recently released would fundamentally alter the regulatory landscape for the review and oversight of LDTs and the clinical labs that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 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:]

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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 risk 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 Investigation 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 great--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 cross 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 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 2 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.

[The prepared statement of Mr. Pallone follows:]

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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.

Dr. {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 would we--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 amongst 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 laboratory-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 follows:]

This is a preliminary, unedited transcript. The statements within may be inaccurate, incomplete, or misattributed to the speaker. A link to the final, official transcript will be posted on the Committee's website as soon as it is available.

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Dr. {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 the--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 this--a copy of this legislation for the record also.

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

[The prepared statement of Dr. Burgess follows:]

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Mr. {Pitts.} Without objection, so ordered.

[The information follows:]

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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 Help, 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.

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^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 encourage 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.

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 of--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 crated 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 hurts 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:]

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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 4 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 to 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 particularly has 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 that--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 have 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.

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.} Okay. 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 totally--they are 2 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.} Yeah, so we--I mean 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 do the--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 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, okay, 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.} Chair thanks the gentleman.

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

Dr. {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.

Dr. {Burgess.} But all internal documents that you have received at the FDA that formed the basis of this decision, may you--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.

Dr. {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.

Dr. {Burgess.} So those would be the specifics that we would be asking for.

Now, you know, we have kind of 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 able to provide.

Dr. {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--

Dr. {Burgess.} You--

Dr. {Shuren.} --public, very collaborative.

Dr. {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 discussion--decision?

Dr. {Shuren.} Actually, we have been consistent for years that we do regulate LDTs. I mean 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 a--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 requirement that isn't already imposed upon the labs, but simply we have not been enforcing.

Dr. {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. {Suren.} 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, you know, we have been talking about exercise--enforcing those requirements in LDT as the existing requirement since the 1990's. We have been called upon by the Department of Energy. We had 2 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, seven years later, that is what we are doing, four 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.

Dr. {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.} Chair thanks the gentleman.

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 they are subject--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 we--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 provide--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--it is clearly 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.

Dr. {Burgess.} Does the gentleman yield for the last few seconds?

Mr. {Griffith.} You got it.

Dr. {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--

Dr. {Burgess.} Will you collect user fees from those labs?

Dr. {Shuren.} For which ones?

Dr. {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 is--was put into MDUFA III when we did this with the device industry was specifically for that purpose, that if we exercised--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.

Dr. {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.

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. Would you--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.} Okay. 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 on 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.} Okay.

Dr. {Shuren.} --and user fee discussions.

Mr. {Green.} Okay. 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 what--at what point is LDT a medical device when it--when does its use, interpretation, application and modification become a service provided by a pathologist of 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 complimentary 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.} Okay. 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, you know, 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 have--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, you know,

discretion is important and the partnership between the two agencies is really important and--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.

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, we--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 a--specifically about that, but there is a new era coming in health care delivery and the like, and I am--I just wanted to report back that that was a very productive hearing we had this June.

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 in consistent 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 diagnosis--diagnostic or patient treatment claims--well, I think you have kind of--

would be permissible, and what kinds of evidence would be required by the FDA?

Dr. {Shuren.} Yeah, so in terms of, you know, permissible, one would be permissible without coming to the FDA, and we have kind of 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 filling 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.

Now recognizes 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 CLA--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 follows:]

********** COMMITTEE INSERT **********

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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 system--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 finding 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 that--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, you know, 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 complimentary.

Ms. {Schakowsky.} So I just have a couple of--so how do you plan to coordinate then with CMS to make sure that, you know, we are getting the best data?

Dr. {Shuren.} Yeah, so we already work with CMS. We have a very close relationship. We are part of the CLIA program. When you--they talk about, you know, to make an LDT you have to be in a high complexity lab, you know, 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.} Um-hum.

Dr. {Shuren.} --and our plan is not to duplicate those requirements, it is to just go with the pieces that are complimentary. 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.} Chair thanks the gentlelady.

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 kind of clarify some of the comments that--the responses that you have given to some of the questions, because I--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.} Okay, so--

Dr. {Shuren.} --the device tax.

Mrs. {Ellmers.} --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 by the, you know, 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 in--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.} Okay, 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 the--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 those--that authority to do that.

Mrs. {Ellmers.} Now, you have the authority--

Dr. {Shuren.} Right.

Mrs. {Ellmers.} --but you can't say definitively today that that is not going to happen, correct? I mean--

Dr. {Shuren.} That--

Mrs. {Ellmers.} --that could be changed at any moment. You could--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. That is--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.} Um-hum.

Dr. {Shuren.} --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, you know, kind of the--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.} And what--I mean where did that come from, what statute, when and, you know, when did it become part of your--the ability for the FDA to institute this?

What--can you go back, give us a date, a time, a rule, a--

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.} Okay, 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.} Yeah, and keep in mind, we have been looking at this for years. We have had these discussions, you know, starting in the 1990's, 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, it is because the tests have changed. I mean 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.} We--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.

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. Suren, 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 their--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 should--they are supposed to be validating those tests when we--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 rulemaking?

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 though 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, okay, 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 have--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.} The--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 of--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 was or will be in their development and use?

Dr. {Shuren.} Okay. 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 shouldn't. 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, you know, 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. Besides the 2008 statement by the Advisory Committee on Genetics, Health and Society that there have been a few--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.} Yeah. 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 doesn't--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 complimentary systems, and in going forward, we need to make sure we are coordinated and we avoid any duplication, but they are complimentary systems. And, you know, 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. In--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 approved their-- 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.} --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.} 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 is 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 issue--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, you know, 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 it is--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.} Yeah, and, you know, 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 changed 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.} Yeah, so this provision pertains to labs when they are using tests. It does not pertain to when they are manufacturing--

Mrs. {Blackburn.} Okay.

Dr. {Shuren.} --tests. That is the distinction. And I also, you know, am 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 know, 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 1990's. 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 be--not have the gray hair.

Mrs. {Blackburn.} Well, we are--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.} Yeah, I just ask--

Mr. {Pitts.} I am trying to get those--

Ms. {Eshoo.} You mean you weren't paying--

Mr. {Pitts.} --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.} --so ordered.

[The prepared statement of Ms. Eshoo follows:]

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Ms. {Eshoo.} Dr. Shuren, it is good to see you, as always.

I think, you know, 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 there is--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, you know, 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.} --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 understand something, that, to me, suggests some kind of

complexity that is deep and broad.

Dr. {Shuren.} Yeah, and that is--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.} Um-hum.

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. Uh-huh.

Dr. {Shuren.} Yes.

Ms. {Eshoo.} Yeah.

Dr. {Shuren.} And then in terms of, you know, with innovation, one thing I will say is innovation isn't just

something new--

Ms. {Eshoo.} Um-hum.

Dr. {Shuren.} --it is also value--

Ms. {Eshoo.} Um-hum.

Dr. {Shuren.} --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.} Um-hum.

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.} Um-hum.

Dr. {Shuren.} So how do we strike that balance on innovation--

Ms. {Eshoo.} Um-hum.

Dr. {Shuren.} --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.} 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.

Dr. {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, okay, 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 you have not--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 progressing--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, you know, the holdup at OMB, the holdup was not--wasn't overdoing an economic analysis on this. They had--

Dr. {Burgess.} Is that not part of OMB's job to look at the economic impact of changes made by the agencies--

Dr. {Shuren.} They--

Dr. {Burgess.} --just as a general rule?

Dr. {Shuren.} They do that in rulemaking for certain rule when they review those.

Dr. {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--

Dr. {Burgess.} Okay, well--

Dr. {Shuren.} --in 2007.

Dr. {Burgess.} But back to the question of the economic impact.

Dr. {Shuren.} Um-hum.

Dr. {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.

Dr. {Burgess.} Thank you, Mr. Chairman. I will yield back.

Mr. {Pitts.} Chair thanks the gentleman.

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 '80's, 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, you know, 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, you know, we need to achieve the right balance, but I appreciate it.

Thank you, Mr. Chairman.

Mr. {Pitts.} 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--

[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 InVitae 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 follows:]

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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.

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^STATEMENTS OF ANDREW FISH, EXECUTIVE DIRECTOR, ADVAMED DIAGNOSTICS; KATHLEEN 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

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^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' office, clinics--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 advance, complex and high-risk tests, and under our current oversight paradigm, LDTs are not reviewed for safety and effectiveness, when the same test 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 decision 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 force 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:]

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Mr. {Pitts.} Chair thanks the gentleman.

Now recognize Dr. Behrens Wilsey 5 minutes for an opening statement.

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^STATEMENT OF KATHLEEN BEHRENS WILSEY, M.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 advanced new--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 innovative 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 capitals appreciate that there are significant differences between the 2 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:]

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Mr. {Pitts.} Chair thanks the gentlelady.

Now recognize Mr. Mertz 5 minutes for opening statement.

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^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 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 in--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 2 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:]

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Mr. {Pitts.} Chair thanks the gentleman.

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

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^STATEMENT CHRISTOPHER NEWTON-CHEH, M.D.

} Dr. {Newton-Cheh.} 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 Madison and 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 they--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 of these products--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 test 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 HA 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:]

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Mr. {Pitts.} Chair thanks the gentleman.

Now recognizes Dr. Sawyers 5 minutes for opening statement.

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^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 ACR, 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 is all, you know, 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-lead 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 what--why am I here today to talk about LDTs? Well, it is obvious, because diagnostics are critical to the success of this targeted cancer 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 over--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 ae 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 assure--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:]

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Mr. {Pitts.} 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 follows:]

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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 have 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 recent--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 inspections, 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 all of you--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. That is our--we--so we share that opinion with FDA.

Mr. {Pitts.} Okay, 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 '90's, 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 not--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 it--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.

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 LTD--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 whether 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 has--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.} Okay. 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 we--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, it is a--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 2 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--the original HIV test back in 1987, which was approved, is--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.} Okay, 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 much--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 the--including 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 Food--federal Food and Drug and Cosmetic Act in 1976 to give the FDA authority over in vitro diagnostics, IVTs. Can you describe what the differences there is, 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, 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 in--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 I--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.} Chair thanks the gentleman.

Now recognize the Vice Chairman, Dr. Burgess, 5 minutes

for questions.

Dr. {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, well, 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 I greatly appreciate--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 will have to--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.

Dr. {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 at the--at 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--

Dr. {Burgess.} Dr. Behrens Wilsey.

Ms. {Behrens Wilsey.} I apologize.

Dr. {Burgess.} Yeah.

Ms. {Behrens Wilsey.} I--

Dr. {Burgess.} From the investor's perspective, this discrepancy between number of tests coming around and the number of approvals, if the FDA's grasps is indeed increased, what does that do to the viability of the--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.

Have 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.

Dr. {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 develop--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 reasons why this area does not have the same number of investors as the pharmaceutical area.

Dr. {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 even--when President Obama was Senator Obama and he introduced the bill that I put into the record this morning, it was--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 IVDMIA. 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 all--Stanford 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.

Dr. {Burgess.} Okay, thank you, Mr. Chairman. I yield back.

Mr. {Pitts.} 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 follows:]

********** COMMITTEE INSERT **********

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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.} Okay, 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, you know, second generation tests is an important detail. I can't be

so--such a high bar that it impairs or harms, you know, second, you know, followers from joining in, but I see that, you know, 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. The, you know, as--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 that can't be easily compared with other labs. So a more uniform sort of trust in the sensitivity and specificity of tests would accelerate the post-approval understanding of who--what patients are most likely to benefit from what drugs.

In terms of harm, you know, the examples have been given earlier of tests that didn't, you know, hold up to the light of day later on in subsequent publications, as made by, you know, 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.} Yeah, 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 2 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.} Chair thanks the gentleman.

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

Mr. {Bilirakis.} Yeah, I guess it is working, okay.

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 then. 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 the--some of those who make that argument that it is unregulated, it is actually a bit of a myth because it is--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 thing I want--point I want to make is that the--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. A pap smear--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. We are--if you look at the regulations under CLIA, labs, they do, they regulate them as labs. The personnel, the procedures, the specimen collection, the validity--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 of--or a third regulation to laboratories is not leveling the playing field, it is making--we are on 2 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, that could be--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.} Chair thanks the gentleman.

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 different--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--that they should be handled differently?

Mr. {Fish.} AdvaMed Dx's position currently is that currently 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. We--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 if--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 before--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.} Okay, 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.

Dr. {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--for the budget as to the financial impact. So, you know, 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, why not proceed with actual--if the onus is so severe, why not proceed through a regulatory pathway through the--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.

Dr. {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.

Dr. {Burgess.} --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.

Dr. {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?

Dr. {Burgess.} Scalability--

Mr. {Mertz.} Yeah.

Dr. {Burgess.} This--you are--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, I mean 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 5 time -- a fivefold increase in the number of PMAs they would be doing in the first year. There are no--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, you know, the regular manufactured kits, so we are very concerned about that. And I also--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 they are, and then it will expose the impact it will have on the laboratory industry and the FDA.

Dr. {Burgess.} Thank you, Mr. Chairman, and I will yield back.

Mr. {Pitts.} Chair thanks the gentleman.

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.} Yeah, 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.} Um-hum.

Dr. {Sawyers.} --I think it is an unknown.

Mr. {Waxman.} And, Dr. Newton-Cheh, how do you respond? Same question.

Dr. {Newton-Cheh.} I--it is completely opaque. I mean 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.} Yeah. 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 LTD [sic] 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, you know, 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 standalone, independent laboratories developing tests that are outside the context of patient care. And those--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 and--the cases, or do you think there ought to be a rulemaking, every LTD 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.} Yeah.

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.} Um-hum.

Ms. {Behrens Wilsey.} --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.} --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.} Um-hum.

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, I think, 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.} 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.]