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STATEMENT

OF

JEFFREY SHUREN, M.D., J.D.

DIRECTOR

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

FOOD AND DRUG ADMINISTRATION

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

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INTRODUCTION

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

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

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

EVOLUTION OF LABORATORY DEVELOPED TESTS (LDTS)

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

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

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

The need for additional FDA oversight of LDTs has been discussed since the mid-90s. The Department of Energy, the National Institutes of Health, two different advisory committees to the Health and Human Services Secretary, and the Institute of Medicine, have recommended additional oversight of LDTs and identified FDA as the agency to provide such oversight[1]. This

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

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

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

Institute of Medicine. *Evolution of Translational Omics: Lessons Learned and the Path Forward*. Washington, DC: The National Academies Press, 2012.

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

RISK-BASED, PHASED IN APPROACH FOR TAILORED OVERSIGHT

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

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

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

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

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

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

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

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

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

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

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

FDA OVERSIGHT IS IMPORTANT FOR INNOVATION

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

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

PERSONALIZED MEDICINE

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

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

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

CONCLUSION

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

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

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