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Food and Drug Administration

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STATEMENT

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Examining the Regulation of Diagnostic Tests and Laboratory Operations

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INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Jeff Shuren, Director, Center for Devices and Radiological Health, or CDRH, at the Food and Drug Administration (FDA or the Agency). I am pleased to be here today to discuss the importance of diagnostic tests in medicine and FDA's role in assuring the reasonable safety and effectiveness of these tests; that they are accurate, reliable, and clinically meaningful—regardless of where they are produced—so that patients and their health care providers can rely upon their results to make major medical decisions.

FDA's Statutory Framework for Diagnostic Tests

How the Device Framework Applies to in vitro Diagnostic Devices (IVDs)

IVDs are tests used in hospitals, doctors' offices, laboratories, and in the home to help health care providers and patients to make the best care management decisions possible, based on accurate, reliable information about a patient. IVDs can be used in the context of acute outbreaks, such as the recent Ebola outbreak, and in the management of chronic diseases like cancer and diabetes. IVDs are a cornerstone of precision medicine, allowing doctors to target therapy to those most likely to respond and avoid unnecessary treatment for those who won't. Because our health care system depends on good information to deploy advanced therapies and new scientific insights into disease and wellness, the success of modern medicine depends on the availability of accurate, reliable diagnostic tests.

FDA regulates IVDs under the flexible, risk-based framework that was put in place by the Medical Device Amendments of 1976 (MDA), which applies to all medical devices intended for human use. Under this framework, FDA assigns IVDs to one of three classes that correspond to the level of risk the IVD presents to patients and the public:

- Class I IVDs encompass about half of all IVDs; these present the lowest level of risk and generally do not require any premarket review by FDA. An example of a Class I IVD is a test system to measure urinary pH.

- Class II IVDs present a moderate level of risk and are generally subject to premarket review; however, they may be exempted when premarket review is not necessary to provide reasonable assurance of safety and effectiveness. Examples of Class II IVDs include blood glucose test strips used by people with diabetes and tests to help doctors diagnose heart failure.

- Class III IVDs present the highest level of risk and are subject to premarket approval and other regulatory controls to ensure these tests can be used safely and effectively. Examples of Class III IVDs include diagnostic tests used to match ovarian cancer patients with a drug regimen.

The primary risk IVDs pose is the risk of an undetected inaccurate test result: a false-positive test result that is not detected could lead to harm from unnecessary medical procedures, delay of necessary medical procedures, and emotional distress. A false-negative result that is not detected could lead to injury, and even death, from unchecked progression of disease, and could have

serious public health ramifications from the preventable transmission of infectious disease. Each of these false outcomes also could result in increased health care costs.

Examples of tests that FDA considers high risk are companion diagnostics that help with the selection of specific treatments for specific patients; with these diagnostics, a faulty test could deprive a patient of a potentially lifesaving therapeutic or could cause a patient to be given an ineffective drug, delaying treatment with the appropriate therapy. An example of a moderate-risk test would be a blood test to aid in the diagnosis of heart failure in the emergency department. Erroneous results from this type of test could also delay appropriate treatment. In both cases, the Agency's premarket review and post-market controls are essential to ensuring patients don't experience grave consequences from inaccurate results. Examples of tests that FDA considers the lowest level of risk include tests for ovulation or certain vitamin deficiencies; we believe about half of all IVDs fall into this category and, as such, we do not require pre-market review.

Under its medical device framework, FDA seeks to apply the level of regulation necessary to establish a reasonable assurance of safety and effectiveness for IVDs, as it does for medical devices generally. For IVDs subject to premarket review, a reasonable assurance of safety and effectiveness generally means that, taking into account the analytical and clinical performance information provided by the sponsor, there is a reasonable assurance that the benefits from the test outweigh the risks it poses and that the test will provide clinically significant results. For moderate-risk tests, the review standard is comparative, and FDA determines whether the test's performance is substantially equivalent to that of a predicate device. And, in cases where there is no existing predicate, novel, moderate-risk tests, if safe and effective, can come to market through our *de novo* down-classification pathway. For high-risk tests, premarket approval is

based on an independent demonstration of safety and effectiveness. *Analytical performance,* also referred to as *analytical validity,* refers to how well the test can detect or measure certain markers in human specimens. *Clinical performance,* also referred to as *clinical validity,* refers to whether the marker has clinical significance, meaning the marker correlates with a disease or condition or with the ability to predict a therapeutic response to a drug.

This assurance of safety and effectiveness is just as important when tests are modified. Modifications are changes that are made by laboratories and other manufacturers to IVDs, and range from simple changes that may not affect the analytical or clinical performance of the test, such as modifying the salt used in a buffer solution, or making an increase in the number of samples that a laboratory analyzer can process at one time, to highly complex modifications that affect a test's performance—such as changing the measuring range of a marker to detect lower levels or adding a new marker to a panel of markers—or a test's intended use, such as changing the intended use of a Hemoglobin A1c test from monitoring glucose control in someone who already has diabetes to using that test to diagnose diabetes. FDA does not review the vast majority of modifications made to IVDs, or medical devices generally, by manufacturers. However, when a change is critical and affects or could significantly affect the safety or effectiveness of the device—for example, the change elevates the risk of a test or changes the test performance or intended use—it is critical for patients that FDA review the changes to make sure that the test still works. Without oversight, such critical modifications could result in a significant increase in incorrect results. And they could pose the same risk that patients will be exposed to unnecessary treatments or may delay or forgo treatment altogether.

FDA's evidentiary standard for premarket review of devices, including IVDs, is valid scientific evidence—a standard established by Congress in 1976 that still sets the benchmark for

evidence to support premarket submissions. This benchmark ensures that the evidence is of sufficient quality that it can be relied on to determine whether a device should be approved or cleared. Although valid scientific evidence includes prospective clinical trials, the majority of IVDs come to market based on studies using existing human specimens and do not require prospective clinical trials.

How FDA Has Adapted its Oversight to Emerging Diagnostic Technologies

FDA has been highly adaptive with its authority over IVDs, particularly in responding to new diagnostic technologies. FDA has provided clear guidance for companion diagnostics and has suggested a flexible and adaptive regulatory approach for Next-Generation DNA Sequencing devices. These approaches demonstrate the adaptability of the existing regulatory framework and the responsiveness of FDA's device program to regulatory issues presented by these new technologies.

Companion Diagnostics: Companion diagnostic tests play an important role in promptly determining which therapies may be safe and effective for a particular patient, and they are a key component of precision medicine. FDA has approved more than 20 companion diagnostic tests, all of them within the user fee performance goals, ensuring the timely marketing authorization of both the device and drug components. In 2014, FDA issued final guidance describing a clear regulatory pathway for developers of companion diagnostic tests and pharmaceutical manufacturers, receiving strong support from both pharmaceutical and conventional test manufacturers for providing regulatory clarity in this rapidly advancing area of medicine.

Companion diagnostics approved by FDA in recent years include the BRACAnalysis CDx™ test, a laboratory developed test that aids in identifying ovarian cancer patients who may respond

to the drug Lynparza™ (olaparib), based on certain BRCA variants; the THxID™ BRAF Kit, which detects certain mutations in melanoma tissue samples to aid in selecting patients for drug therapy with Tafinlar® (dabrafenib) or Mekinist™ (trametinib); and the therascreen® KRAS RGQ PCR Kit, a test that screens out colorectal cancer patients with genetic mutations known to predict a non-therapeutic response to the biological products Erbitux® (cetuximab) and Vectibix® (panitumumab).

Next-Generation Sequencing: Many newly developed genomic diagnostic tests rely on next-generation sequencing (NGS), an advanced technology, which is poised to become a keystone of precision medicine. NGS tests can rapidly generate an unprecedented amount of genetic data for each patient. Most IVDs are used to detect a single or a defined number of markers to diagnose a limited set of conditions; in contrast, NGS tests can identify thousands or millions of genetic variants in a single run that can be used to diagnose or predict the likelihood of an individual developing one or more of a variety of diseases. An example that demonstrates the potential of NGS for diagnosing disease is the approach FDA has taken for tests to detect mutations that cause cystic fibrosis. FDA provided marketing authorization for an NGS test for cystic fibrosis using innovative approaches to establishing the test's effectiveness in an effort to reduce regulatory burden while continuing to ensure safety and effectiveness. This approach can allow FDA to leverage existing data in high-quality, curated genetic databases as an alternative to conducting new clinical trials, and require targeted analytical performance data for only a subset of variants that would be representative of the device performance.

In summary, the central features of FDA's framework for devices, including IVDs, are a system of device classification that tailors regulation to device risk; a transparent review standard that accounts for the benefits and risks to patients, and range of regulatory controls that together

provide a reasonable assurance of safety and effectiveness; and an adaptive but scientifically grounded evidentiary standard of valid scientific evidence. Patients have benefited from this regulatory model, which has enabled FDA to respond to innovation in rapidly emerging technologies, such as NGS, while ensuring tests used to make treatment decisions for patients are accurate and reliable. To ensure that our health care system continues to benefit from reliable and accurate diagnostic tests, FDA's regulation of IVDs should retain these basic features, including with respect to instances when tests are modified.

FDA's Proposal for Oversight of Laboratory Developed Tests (LDTs)

LDTs are IVDs intended for clinical use and designed, manufactured, and used within a single clinical laboratory. LDTs have all of the same potential uses in health care that IVDs manufactured by traditional manufacturers and approved or cleared by FDA have; like other IVDs, LDTs are used to diagnose conditions, to manage disease, and to gather genetic information to determine the best course of treatment for a patient. Today, many companion diagnostics and other high-risk tests are developed by laboratories. Modern LDTs are often complex, have a nationwide reach, and have high-risk uses, and without oversight could present risks for patients and health care providers who rely on the results of LDTs to make medical decisions. In these respects, LDTs today differ from the relatively simple LDTs in use at the time of the Medical Device Amendments (MDA) of 1976. In many cases, the only difference between many modern LDTs and other IVDs is where they are manufactured, and the accuracy and reliability are every bit as important for modern LDTs as for any other IVD.

Currently, FDA exercises enforcement discretion concerning premarket evaluation and other requirements for LDTs. As such, the Agency generally does not review such tests for clinical

validity prior to such tests being marketed, nor does the Centers for Medicare & Medicaid Services (CMS). While under the Clinical Laboratory Improvement Amendments (CLIA), CMS provides oversight over the pre-analytic, analytic, and post-analytic policies and procedures for laboratory testing on human specimens for medical purposes, and provides minimum standards for the personnel involved in such testing. CMS generally does not delve into ensuring the clinical validity of testing (as CLIA regulates how and by whom the test is conducted and reported out, rather than the scientific principles behind or the clinical validity of the test system itself).

Given the increased complexity of LDTs and the importance of their role in contemporary medical decision-making, FDA issued draft guidance documents describing how it intends to enforce its authorities with respect to LDTs. Examples of concerns that arise from LDTs that are not reviewed for reasonable assurance of safety and effectiveness include the implications for patients who may get incorrect results from faulty tests. For example:

- Ovarian cancer tests have been developed by labs without proper validation to show that the variant they detect is clinically meaningful, and some have been used in clinical practice in the United States. Some of these tests provide very high numbers of false-positive results; some continue to make inflated claims concerning clinical benefit, even after comprehensive evaluations of women with ovarian cancer have failed to find any link between the disease and the genetic variant identified by the LDT. Women who received false-positive results from these tests may have had unnecessary, major surgery to remove their ovaries.

- There are currently on the market several LDTs that test for KIF6, a genetic variant postulated but not proven to predict coronary heart disease (CHD) and the likelihood that a patient will benefit from statins—drugs that reduce the risk of heart attack and death from CHD. Statins also carry side effects that can include muscle pain, cramping, nerve damage, mood, sleep, and cognitive impairment, and, rarely, muscle breakdown leading to kidney failure. One lab sought FDA approval for its KIF6 test; however, FDA determined that a meta-analysis of 19 studies did not support the clinical validity of KIF6, meaning that the data did not adequately support a link between the genetic variant or response to statin therapy. FDA estimates that over 150,000 patients have been given this test; as a consequence, many were likely over- or undertreated with statins. FDA estimates that this resulted in a cost of over $2.4 billion.

Public health concerns raised by these and other examples of defective LDTs require that FDA implement a more proactive oversight policy. The public must be assured that the tests used in the provision of health care, whether developed by a laboratory or other manufacturer, are accurate and reliable. IVD tests come to FDA for review, in part to try to detect such problems before patients are exposed to them. In light of these concerns, in 2014, after providing a notification to Congress as required by section 1143 of the Food and Drug Administration Safety and Innovation Act of 2012, FDA issued draft guidance documents describing how it intends to enforce its authorities with respect to LDTs.

The draft oversight guidance proposes to phase in enforcement of premarket review requirements for higher-risk LDTs, such as those used to guide treatment decisions, including the many LDTs with the same intended use as cleared or approved companion diagnostics, and proposes to delay

enforcement of the Quality System regulation, at least until the time of enforcement of premarket requirements. In addition, under the draft oversight guidance, FDA would continue to exercise enforcement discretion, with respect to premarket review requirements for low-risk LDTs and LDTs for rare diseases, among others; sponsors of these tests would still need to notify FDA that these LDTs are being offered, as well as providing reports of any adverse events, but would not generally come for premarket review. FDA believes that roughly half of all LDTs would be considered low risk. FDA oversight would be phased in to accommodate lab preparation and transition time. The draft guidance regarding notification and medical device reporting describes an option for clinical laboratories to notify FDA of the LDTs that they manufacture, in lieu of registration and listing, and describes the Medical Device Reporting requirements for clinical laboratories manufacturing LDTs. FDA believes the flexibility built into its proposed approach to LDT oversight is a critical feature of any LDT oversight model.

FDA has completed its review of the public comments on the draft guidance documents that it received through an open public docket and a two-day public meeting, as well as feedback received from several webinars FDA held with stakeholders to discuss concerns and address questions. In response to feedback from stakeholders, FDA is taking several other actions, including:

- High-level engagement with CMS to strengthen coordination of laboratory oversight. FDA also intends to produce a draft guidance document on its quality system requirements for LDTs, to provide clarity for laboratories on how they can leverage compliance with CLIA requirements to satisfy those applicable FDA guidelines;

- Together with CMS, meeting with each of the accrediting organizations and CLIA-exempt state laboratory programs, to identify any potential overlaps between CMS and FDA activities in this area and evaluate if there are areas for streamlining; and

- Ongoing meetings with stakeholders, including laboratories, patients, traditional IVD manufacturers, and medical practitioners.

FDA is committed to developing a final policy for oversight of LDTs that encourages innovation, improves patient outcomes, and strengthens patient confidence in the reliability of these products.

CONCLUSION

I thank the Subcommittee for its leadership in calling this hearing to address the critical role of diagnostic tests in American health care. Mr. Chairman, this concludes my formal remarks. I am pleased to answer any questions the Subcommittee may have.