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STATEMENT OF

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INTRODUCTION

Good morning, I am Dr. Jeff Shuren, Director of the Center for Devices and Radiological Health (CDRH or the Center) at the Food and Drug Administration (FDA or the Agency). I am pleased to be here this morning to explain FDA's recent activities related to direct-to-consumer (DTC) genetic tests and our future plans for the regulation of laboratory-developed tests.

Scientific advances resulting from the Human Genome Project completed in 2003 have expanded our understanding of the genetic contribution to health and disease. These advances have also resulted in the development of new tests that can better identify individuals at risk for particular medical conditions and target medical treatments based on the likelihood that a patient will respond or experience an adverse event based on their individual genetic profile. FDA supports the promise and development of innovative genetic tests.

As Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, and Francis S. Collins, M.D., Ph.D., Director of the National Institutes of Health, note in their jointly authored article entitled "The Path to Personalized Medicine," published in the June 15, 2010, *New England Journal of Medicine*, "Major investments in basic science have created an opportunity for significant progress in clinical medicine. Researchers have discovered hundreds of genes that harbor variations contributing to human illness, identified genetic variability in patients' responses to dozens of treatments, and begun to target the molecular causes of some diseases. In addition, scientists are developing and using diagnostic tests based on genetics or other

molecular mechanisms to better predict patients' responses to targeted therapy.... Together, we have been focusing on the best ways to develop new therapies and optimize prescribing by steering patients to the right drug at the right dose at the right time."

However, Dr. Hamburg and Dr. Collins also note that the field of personalized medicine will not make good on that promise if the *in vitro* diagnostic tests on which practitioners and patients rely to inform treatment decisions are inaccurate or the link between what the test measures and its clinical significance is tenuous. Failure to validate the accuracy, reliability, and clinical implications of a test can result in patient harm from misdiagnosis, failure to treat, delay in treatment, inappropriate treatment, or avoidable adverse events.

OVERVIEW OF FEDERAL REGULATION

Congress gave FDA explicit authority to regulate medical devices, including *in vitro* diagnostic tests, in the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act). *In vitro* diagnostic devices (IVDs) are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or conditions arising from a disease. Genetic tests are a type of IVD.

Under the Act, FDA assigns medical devices to one of three "classes" based upon their attendant risks. The level of regulation applied to IVD devices is based primarily upon risk to the patient of an undetected incorrect test result.

- Class I, subject only to general controls applicable to all devices, is the lowest risk category for a device. Class I IVDs include certain reagents and instruments, as well as a number of highly adjunctive IVD tests, where one test is dependent on the results of another; consequently an incorrect result would generally be detected easily. Most Class I devices are exempt from premarket review. An example of a Class I test is a luteinizing hormone test that, if it gives a false result, may lead to delayed conception but is unlikely to directly harm the patient.
- Class II, generally subject to general controls and special controls, is the moderate-risk category for a device, and includes many standard laboratory tests, such as chemistry and immunology tests. Most Class II tests are subject to FDA review through premarket notification under section 510(k) of the Act. For example, a false sodium result (a Class II test) may be life-threatening if the error is unrecognized and treatment decisions to correct the sodium level are made based on the false result.
- Class III, subject to premarket approval requirements, is the highest risk category for a device and includes devices and tests that present a potentially unreasonable risk of illness or injury. For example, a false negative result for a hepatitis C virus test (a Class III test) may result in failure to provide appropriate treatment, leading to risk of liver failure due to delayed treatment. In addition, without the knowledge that he or she is infected, the patient may put others at risk by spreading the disease.

Many IVD tests are Class II or Class III devices, and some also may be biological products subject to section 351 of the Public Health Service Act. In addition to premarket controls, the FD&C Act provides FDA with authority to perform post-market review, and monitor adverse events or even mandate a recall if, based on adverse event reports or other data, there is a

reasonable probability that a test could cause serious adverse health consequences or death in clinical use.

Federal oversight of IVDs includes oversight of laboratories that perform these tests by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), and the Federal Trade Commission (FTC) under the Federal Trade Commission Act (FTCA). Under CLIA, CMS regulates laboratory testing activities performed on humans in the United States for health purposes, covering more than 200,000 laboratory entities. FDA's role under CLIA is to categorize commercially marketed IVDs in terms of their complexity. This complexity categorization determines the stringency of requirements to which the laboratories performing the tests are subject and the attendant personnel education, training, and skill level required.

CLIA and FDA regulations complement one another. CLIA regulations focus on the quality of the clinical testing process, such as laboratory quality control; i.e., daily check that the test is working, external accuracy checks, credentials of laboratory personnel, and documentation of laboratory procedures. FDA regulations address the safety and effectiveness of the diagnostic tests themselves and the quality of the design and manufacture of the diagnostic tests.

Section 5 of the FTCA prohibits unfair or deceptive acts or practices in or affecting commerce. Section 12 of the FTCA specifically prohibits the dissemination of false advertisements for foods, drugs, devices, services, or cosmetics. The FTC analyzes the role of advertising in bringing health-related information to consumers and can bring law enforcement actions against false or deceptive advertising.

OVERVIEW OF FDA REGULATION OF GENETIC TESTS

The purpose of genetic tests includes predicting risk of disease, screening newborns, directing clinical management, identifying carriers, and establishing prenatal or clinical diagnoses or prognoses in individuals, families, or populations. To date, 353 U.S. laboratories have listed themselves on a voluntary website that provides information about laboratories offering genetic tests, but estimates are that there may be as many as 700 laboratories offering such tests.

A genetic test is only subject to FDA oversight if it is a medical device; that is, if it is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease. For example, a test to determine a person's risk of developing heart disease is a device, whereas a test to determine ancestry is not a device. The type of genetic testing has changed over the past two decades. Whereas early tests tended to identify a single genetic mutation and a patient's risk for developing a disease, some newer tests evaluate thousands of genes or the entire genome and report out risk for a disease based on the combination of dozens of genetic variations.

There currently are two paths to market for a genetic test used in clinical management of patients, as is the case for other IVDs. One is through development of a commercial test kit by an IVD device manufacturer for distribution to multiple laboratories. The Agency has exercised its regulatory authority over these products and has approved several tests for specific genetic factors.

The second pathway is through the development of a test by a laboratory for use only by that laboratory; these are commonly called laboratory-developed tests (LDTs). Conservative estimates are that there are between 2,500 – 5,000 LDTs, including genetic tests that are developed and offered by hundreds of different laboratories.

FDA has the authority to regulate LDTs as it does all IVDs. The extent of FDA oversight of an IVD, such as a genetic test that meets the definition of a device, is based on the risk of an inaccurate result from the test, not who makes the tests or their business models. However, although FDA has the authority to regulate LDTs, FDA has generally exercised enforcement discretion since the device law was passed in 1976. At that time tests made by laboratories were generally low-risk diagnostic tools or relatively simple, well-understood tests that diagnosed rare diseases and conditions, and which were more dependent on expert interpretation. Therefore, the accuracy of the results was more dependent on the expertise of the pathologist/laboratorian than on the design of the test. Furthermore, these LDTs were used by pathologists/laboratorians and the results reported to physicians within a single institution where both professionals were actively involved in the care of the patient being tested. Most genetic tests being offered today are LDTs.

The nature of laboratory-developed tests has changed over the last 30 years, but most dramatically in the last few years. Today, LDTs are increasingly used to assess high-risk but relatively common diseases and conditions, often are used to provide critical information for patient treatment decisions, rely on novel (sometimes preliminary) scientific findings to support their usefulness, often require complex software and may incorporate automated interpretation in

lieu of expert interpretation, often are used when there are alternative tests available that have been cleared or approved by FDA, and are performed in commercial laboratory settings that are geographically separate from the patient's primary health care professional and health care setting. In addition, some entities marketed their tests without prior FDA review, claiming that they are LDTs, when they are not. Furthermore, the ability of laboratories to market tests without any regulatory oversight creates a disincentive for traditional manufacturers to develop new tests, thereby stifling innovation.

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

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

FDA believes that a test used for patient care should have the same assurances of safety and effectiveness whether it is manufactured for distribution to multiple laboratories or created for use in only one laboratory. Premarket review of moderate and high risk LDTs would ensure that the tests are evaluated for analytical validity and clinical validity, based on their claimed intended use, and would provide an independent and unbiased assessment of the data used to support analytical and clinical claims for those LDTs. This is important because when tests are not well validated, the possibility of incorrect results, which can lead to misdiagnosis or

inappropriate treatment decisions, increases. Premarket review would also ensure that labeling includes the test claims, the data that support those claims, how the test may be interpreted, and the limitations of the test. FDA's post-market surveillance and enforcement tools ensure that tests remain safe and effective once on the market.

In 2001, the Secretary's Advisory Committee on Genetic Testing recommended that "the Food and Drug Administration should be involved in the review of all new genetic tests regardless of how they are formulated and provided." In 2008, the Secretary's Advisory Committee on Genetics, Health, and Society recommended that FDA address all genetic testing using a risk-based approach.

Historically, FDA's oversight of genetic testing has been focused intensively on commercial test kits. The Agency is now engaging in a public dialogue on how it should develop a consistent, reasonable, and fair approach to all genetic tests, whether packaged as kits or provided as LDTs, to ensure safety and promote innovation.

GENETIC TESTS BEING SOLD DIRECTLY TO CONSUMERS

An emerging market segment for the laboratory testing industry is direct-to-consumer testing. A few companies have sought to popularize genetic testing through advertisements and social media. FDA has been aware of these companies marketing to consumers for several years. At the time of the 2006 Government Accountability Office (GAO) investigation of DTC testing, most of these diagnostics were "nutritional genetic" tests—tests to assess what kinds of foods individual consumers should eat and dietary supplements they should take. FDA followed up

with the companies and FDA, CDC, and FTC published a cautionary statement on DTC genetic tests.

New DTC genetic tests subsequently came on the market. FDA met with some of these companies starting in 2007. FDA's Center for Devices and Radiological Health, which is responsible for the oversight of these tests, never informed these companies that they could lawfully market their tests without FDA oversight. Instead, the Center met with these companies to have a better understanding of what the companies were in fact doing or planning to do. Initially their business models were not clear and the tests were being marketed for such purposes as "antiquity determinations." However, since then we have seen changes in the number and types of claims being made. For example, one company provided test reports for 17 diseases, conditions, or traits in 2008 but provided over 100 types of results by 2010. In particular, some companies are making claims about high-risk medical indications, such as determining the risk for cancer or the likelihood of responding to a specific drug. Moreover, in many cases the link between the genetic results and the risk of developing a disease or responding/not responding to a drug has not been well-established.

Marketing genetic tests directly to consumers can increase the risk of a test because a patient may make a decision that adversely affects their health, such as stopping or changing the dose of a medication or continuing an unhealthy lifestyle, without the intervention of a learned intermediary. The risk points up the importance of ensuring that consumers are also provided accurate, complete, and understandable information about the limitations of test results they are obtaining.

Recently, we have seen companies more aggressively market directly to consumers. For example, Pathway Genomics Corporation (PGC) was poised to offer their Pathway Genomics Genetic Health Report, a home use saliva collection kit, directly to consumers through more than 6,000 Walgreen stores. 23andMe is marketing directly to consumers on Amazon.com.

Although FDA has cleared a number of genetic tests since 2003, none of the genetic tests now offered directly to consumers has undergone premarket review by FDA to ensure that the test results being provided to patients are accurate, reliable, and clinically meaningful.

Because of the escalation in risk and aggressive marketing, FDA notified PGC on May 10, 2010, that their offering appeared to meet the definition of a medical device as that term is defined under the FD&C Act, and clearance or approval by the Agency was necessary in order for them to market their product. The test is intended to report the presence or risk of more than 70 health conditions, including pharmacogenetics (prescription medication response), propensity for complex disease, carrier status, and other information from which one could modify one's lifestyle and health regime, supposedly to live a healthier, longer life. These tests have not been proven safe, effective, or accurate, and patients could be put at risk by making medical decisions based on data that has not received independent premarket review. Following receipt of FDA's letter, PGC stopped marketing directly to consumers.

On June 10, 2010, FDA sent similar letters to four other diagnostic test manufacturing firms that were offering their tests directly to consumers (Knome, Inc; Navigenics; deCODE Genetics; and 23andMe). FDA considers all of these products to meet the statutory definition of a medical device on the basis of the manufacturers' claims about the test results For example, the tests

claimed to describe the genetic basis of specific disease traits or conditions on which consumers may base medical decisions; provide personalized information on which medications are more likely to work given a person's genetic makeup; and provide genetic predispositions for important health conditions and medication sensitivities. In addition, a letter was issued to Illumina, Inc. for supplying unapproved reagents and instrumentation (marked "for research use only" and thus not approved or cleared by FDA) to several DTC manufacturers who use the reagents as critical components in their products being offered directly to consumers for clinical, not research, use. These manufacturers generally havenot submitted information on the analytical or clinical validity of their tests to FDA for clearance or approval. All six companies have been invited to discuss the regulatory status of their products further with the Agency. Meetings with the companies are taking place now or have been or are being scheduled. FDA may take additional actions, depending on the outcome of those meetings.

On July 19, 2010, FDA sent similar letters to 15 other firms marketing DTC genetic tests.

PUBLIC MEETING ON LABORATORY-DEVELOPED TESTS

On July 19 and 20, FDA held a public meeting for the purpose of obtaining input from stakeholders on how the Agency should apply its authority to implement a reasonable, risk-based, and effective regulatory framework for LDTs, including genetic tests, in particular, taking into account circumstances unique to LDTs and to avoid any duplication with CLIA. We provided an overview of the history and current regulatory status of LDTs. The meeting discussions focused on:

1. Patient Considerations
2. Challenges for Laboratories
3. Direct-to-Consumer Marketing of Testing
4. Education and Outreach

Each session consisted of presentations from interested stakeholders, followed by an expert panel discussion and question-and-answer period. The meeting record will be held open for an additional comment period of 60 days, after which FDA will collect and review all comments and information presented. Subsequently, the Agency will move forward in developing a draft oversight framework for public comment as quickly as possible. FDA intends to phase in over time whatever framework it constructs, based on the level of risk of the test.

CONCLUSION

Mr. Chairman, I commend the Subcommittee's efforts to inform the ongoing dialog about the safety and accuracy of genetic tests being marketed today. FDA is working toward a reasonable and fair approach to regulation that can give patients and doctors confidence in these tests and facilitate progress in personalized medicine. Mr. Chairman, that concludes my formal remarks. I will be pleased to answer any questions the Subcommittee may have.