Congressional Research Service
Informing the legislative debate since 1914

Regulation of Clinical Tests: In Vitro Diagnostic (IVD) Devices, Laboratory Developed Tests (LDTs), and Genetic Tests

(name redacted)
Specialist in Health Policy

(name redacted)
Specialist in Biomedical Policy

December 17, 2014

Congressional Research Service
7-....
www.crs.gov
R43438

CRS REPORT
Prepared for Members and
Committees of Congress

Summary

In vitro diagnostic (IVD) devices are used in the analysis of human samples, such as blood or tissue, to provide information in making health care decisions. Examples of IVDs include (1) pregnancy test kits or blood glucose tests for home use; (2) laboratory tests for infectious disease, such as HIV or hepatitis, and routine blood tests, such as cholesterol and anemia; and (3) tests for various genetic diseases or conditions. More recently, a specific type of diagnostic test—called a companion diagnostic—has been developed that may be used to select the best therapy, at the right dose, at the correct time for a particular patient; this is often referred to as personalized or precision medicine.

Federal agencies involved in the regulation of IVDs include the Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS). FDA derives its authority to regulate the sale and distribution of medical devices, such as IVDs, from the Federal Food, Drug, and Cosmetics Act and the Public Health Service Act. CMS's authority to regulate IVDs is through the Clinical Laboratory Improvement Amendments of 1988. FDA regulates the safety and effectiveness of the diagnostic test, as well as the quality of the design and manufacture of the diagnostic test. CMS regulates the quality of clinical laboratories and the clinical testing process.

Traditionally, most genetic tests have not been subject to premarket review by the FDA. This is because in the past, genetic tests were developed by laboratories primarily for their in-house use—referred to as laboratory-developed tests (LDTs)—to diagnose mostly rare diseases and were highly dependent on expert interpretation. However, more recently, LDTs have been developed to assess relatively common diseases and conditions, thus affecting more people, and direct-to-consumer (DTC) genetic testing has become more available over the Internet. The extent to which LDTs should be regulated by the FDA, in conjunction with CMS, has traditionally been a subject of debate. Some clinical laboratories and manufacturers of LDTs have maintained that LDTs should be outside of the FDA's regulatory purview. Legislation was introduced in the 110th and 112th Congresses with the aim of clarifying regulatory oversight and supporting innovation.

In June 2010, FDA announced its decision to exercise its authority over all LDTs. A provision in the Food and Drug Administration Safety and Innovation Act of 2012 stipulates that the agency "may not issue any draft or final guidance on the regulation" of LDTs without, "at least 60 days prior to such issuance," first notifying Congress "of the anticipated details of such action." On July 31, 2014, in fulfillment of this statutory requirement, the FDA officially notified the Senate Committee on Health, Education, Labor and Pensions and the House Committee on Energy and Commerce that it will issue draft guidance on the regulation of LDTs, and included the anticipated details of that regulatory framework. On October 3, 2014, the FDA formally issued these documents as draft guidance in the *Federal Register*, giving 120 days for comment.

The draft guidance identifies groups of LDTs that will be (1) exempt from regulation entirely; (2) only required to meet notification and adverse event reporting requirements; and (3) required to meet notification, adverse event reporting, applicable premarket review, and other regulatory requirements. FDA will use the information obtained through the notification requirement to classify LDTs, based on risk, using a public process involving advisory panels and public comment. Once classification has taken place, the FDA will enforce premarket review requirements, prioritizing the highest-risk tests. The agency anticipates the entire process of bringing all LDTs into compliance will take nine years to complete.

Contents

Appendixes

Contacts

Introduction

In vitro diagnostic (IVD) devices, including genetic tests, provide information that is used to inform health care decision making.[1] IVDs are devices that are used in laboratory analysis of human samples and include commercial test products and instruments used in testing, among other things. IVDs may be used in a variety of settings, including a clinical laboratory, a physician's office, or in the home.

IVDs have a number of uses, such as diagnosis, screening, staging, and disease management, including, for example, the selection and dosing of therapeutics. One estimate found that the results of clinical laboratory tests influence approximately 70% of health care decisions.[2] Despite this broad effect on the delivery of health care, spending on IVDs represents a small portion of overall health care costs.[3] The Centers for Disease Control and Prevention (CDC) estimated that, based on 2007 data, approximately 6.8 billion clinical laboratory tests are performed in the United States annually, but noted that "publicly available information about the economic status and quality of the laboratory medicine sector remains limited."[4]

IVDs may be used in the care of a patient in numerous ways (see text box) and at various points in the delivery of care. IVDs differ from other medical devices in that they do not act directly on a patient to produce a result as does, for example, an implantable stent that keeps an artery open to allow blood flow. Instead, the potential for risk of harm to the patient would be from the generation of inaccurate test results that could lead to the mismanagement of a patient's disease or condition (i.e., false negative test result) or to treatment for a disease or condition that is in fact absent (false positive test result).[5]

Given this potential risk, as well as the impact on the overall delivery of health care, the federal government has taken a role in the oversight of IVDs. Federal oversight of IVDs spans several federal agencies, including the Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS). Oversight efforts focus on ensuring the safety and effectiveness of IVDs; the accuracy and reliability of IVDs; the quality of clinical laboratories that carry out IVD testing; the utility of the information in clinician and patient decision making; and the truthfulness of claims made about IVDs that are marketed directly to consumers.

---

[1] The term "in vitro," meaning in glass, refers to testing that is carried out outside of the body. In contrast, "in vivo" testing is carried out in a living organism, such as electroencephalography (EEG), electrocardiography (EKG), or diagnostic imaging (X-ray).

[2] UnitedHealth Center for Health Reform and Modernization, "Personalized Medicine: Trends and prospects for the new science of genetic testing and molecular diagnostics," Working Paper 7, March 2012, http://www.unitedhealthgroup.com/~/media/uhg/pdf/2012/unh-working-paper-7.ashx.

[3] The Lewin Group, "Laboratory Medicine: A National State Report," May 2008, p. 2, https://www.futurelabmedicine.org/pdfs/2007%20status%20report%20laboratory_medicine_-_a_national_status_report_from_the_lewin_group.pdf on October 20, 2012.

[4] Ibid., p. 3.

[5] IVDs evaluate the level of various biomarkers in a patient's tissue or blood sample. A biomarker is used as a surrogate marker for an outcome that is important to patients. The Institute of Medicine defines surrogate as "biomarker intended to substitute for a clinical endpoint [and] expected to predict clinical benefit (or harm ...) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence." Although beyond the scope of this report, recent studies have questioned the wisdom of relying on surrogate markers to accurately predict treatment effects on important clinical outcomes, such as death and quality of life. http://www.iom.edu/Reports/2010/Evaluation-of-Biomarkers-and-Surrogate-Endpoints-in-Chronic-Disease.aspx.

IVDs include genetic tests, a type of diagnostic test that analyzes various aspects of an individual's genetic material (DNA, RNA, chromosomes, and genes).[6] Through basic research, scientists have "discovered hundreds of genes that harbor variations contributing to human illness."[7] They have also found "genetic variability in patients' responses to dozens of treatments" and are using IVDs "to better predict patients' responses to targeted therapy."[8] The use of an IVD companion diagnostic device to select the best therapy, at the right dose, at the correct time for a particular patient is often referred to as personalized medicine.[9] Another term, pharmacogenomics, is sometimes used interchangeably with personalized medicine. Pharmacogenomics is the study of how individual genetic variation affects a person's response to drugs.[10] Currently, more than 100 FDA-approved drugs contain pharmacogenomic information in their labeling.[11]

The Role of IVDs in Health Care

IVDs may be used in many components of the care of an individual patient. These include, for example:

Diagnosing disease or ruling out the presence of a disease;

Predicting the potential risk of eventually developing a disease or disorder;

Determining the likely course or outcomes of a disease;

Choosing the most effective and appropriate treatment;

Guiding disease management; and

Monitoring response to treatment throughout care.

Sources: Raman G., Avendano EE, Chen M. Update on Emerging Genetic Tests Currently Available for Clinical use in Common Cancers. Evidence Report/Technology Assessment No. GEND0511, Rockville, MD: Agency for Healthcare Research and Quality. July 2013.

The regulation of genetic testing has raised several issues. Traditionally, most genetic tests have not been subject to premarket review by the FDA. It has been noted that, in the past, genetic tests were developed mostly by academic or research laboratories primarily for in-house use—tests referred to as laboratory-developed tests (LDTs)—to diagnose rare diseases and were highly dependent on expert interpretation.[12] In recent years, LDTs have been developed to assess relatively common diseases and conditions, such as various cancers. The extent to which all LDTs should be regulated by the FDA has been a subject of debate.[13] On July 31, 2014, the FDA officially notified the Senate Committee on Health, Education, Labor and Pensions and the House

[6] For more information about genetic testing and public policy, see CRS Report RL33832, *Genetic Testing: Scientific Background for Policymakers*, by (name redacted).

[7] Margaret A. Hamburg and Francis S. Collins, "The Path to Personalized Medicine," *The New England Journal of Medicine*, vol. 363, no. 4 (July 22, 2010), pp. 301-304.

[8] Ibid., p. 301.

[9] Food and Drug Administration, *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*, October 2013, p. 6, http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf. For more information about the FDA' s role in personalized medicine, see http://www.fda.gov/scienceresearch/specialtopics/personalizedmedicine/default.htm.

[10] Ibid., p. 8.

[11] Food and Drug Administration, "Table of Pharmacogenomic Biomarkers in Drug Labeling," http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm.

[12] Testimony of Jeffrey Shuren, M.D., Director, Center for Devices and Radiological Health, FDA, in U.S. Congress, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives, *Direct-to-Consumer Genetic Testing and the Consequences to the Public*, hearings, 111th Congress, 2nd sess., July 22, 2010, http://www.fda.gov/NewsEvents/Testimony/ucm219925.htm.

[13] Both the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) in April 2008 and the Secretary's Advisory Committee on Genetic Testing (SACGT) in July 2000 have recommended that FDA be involved in the regulation of laboratory developed genetic tests. For further information on SACGHS, see http://oba.od.nih.gov/SACGHS/sacghs_home.html. For further information on SACGT, see http://oba.od.nih.gov/SACGHS/sacgt_info.html.

Committee on Energy and Commerce that it will be issuing draft guidance;[14] on October 3, 2014, the agency published a notice in the *Federal Register* announcing the availability of the guidance documents and requesting comments within 120 days to ensure their consideration in the development of final guidance. [15]

The appropriate degree and extent of federal regulation of direct-to-consumer (DTC) genetic testing has also been a subject of debate amongst relevant federal agencies as well as the affected entities (mostly for-profit companies, for example, 23andMe, Pathway Genomics, or Life Technologies). Genetic testing has become increasingly available for direct purchase by consumers, generally over the Internet. In this type of testing—direct-to-consumer genetic testing—the consumer sends in a tissue sample, often cells from the inside of the cheek, and the results are conveyed directly to the consumer by the company that developed the test. In 2010, the Government Accountability Office (GAO) testified that in its investigation of DTC genetic tests—priced from $299 to $999—from four companies, it found the DTC genetic test results to be "misleading and of little or no practical use to consumers."[16]

Congress and the regulatory agencies have historically been interested in balancing the goals of allowing consumers to have access, as quickly as possible, to new and improved medical devices with preventing devices that are not safe and effective from entering or remaining on the market. In the case of IVDs, and specifically, LDTs, Congress has introduced bills that attempt to address both of these goals, that is, to support innovation and to increase or expand regulatory oversight.[17] Approaches have included, among others, streamlining regulation by concentrating it in a single federal agency or requiring the FDA to assert its enforcement authority over LDTs.

In addition to its role as regulator, the federal government has a role as a payer for IVDs, primarily through the Medicare program.[18] Medicare covers outpatient clinical laboratory testing and generally reimburses for these tests based on the Clinical Laboratory Fee Schedule (CLFS).[19]

---

[14] Food and Drug Administration, "FDA takes steps to help ensure the reliability of certain diagnostic tests," July 31, 2014, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm407321.htm.

[15] 79 Fed. Reg. 59776, October 3, 2014.

[16] U.S. Government Accountability Office, Direct-To-Consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices, GAO-10-847T, July 22, 2010, p. 4, http://www.gao.gov/new.items/d10847t.pdf.

[17] For example, see (1) 110th Congress: Laboratory Test Improvement Act of 2007, S. 736 (Kennedy); Genomics and Personalized Medicine Act of 2007, S. 976 (Obama); (2) 112th Congress: Modernizing Laboratory Test Standards for Patients Act of 2011, H.R. 3207 (Burgess); and (3) 113th Congress: Medical Testing Availability Act of 2013, H.R. 3005 (Burgess).

[18] Medicare has recently made modifications to its reimbursement mechanism for some IVDs, including molecular pathology tests that are often LDTs. Specifically, "[m]any LDTs do not have their own HCPCS codes; instead, they are billed using unlisted codes for which Medicare Administrative Contractors (MACs) establish a payment amount for their local jurisdictions. Prior to 2012, other LDTs were billed to Medicare using "stacking codes," where a laboratory submits a code for each step of the testing process. These "stacking codes" were eliminated at the end of 2012 and replaced with new test-specific codes." See 78 *Federal Register* 74229, December 10, 2013. The Department of Defense, on the other hand, based upon the new codes, discontinued paying for certain LDTs through the TRICARE program. Under 32 C.F.R. §199.4(g)(15)(i)(A) the Defense Health Agency does not cost-share medical devices including LDTs if the tests are non-FDA approved, which DOD defined as not having received FDA marketing 510(k) clearance or premarket approval. Such non-FDA approved LDTs are not covered by TRICARE, except under a recently promulgated LDT demonstration project. For more information on TRICARE coverage, please contact CRS Analyst Don Jansen.

[19] "Under SSA Sections 1833 and 1861, outpatient clinical laboratory services are paid on a Fee Schedule under Medicare Part B when they are furnished in a Medicare participating laboratory and ordered by a physician or qualified (continued...)

Medicare also covers clinical laboratory testing conducted during inpatient care either in a hospital or a skilled nursing facility (SNF).[20] Although an in-depth discussion of this issue is outside the scope of this report, the federal role as payer intersects with its role as regulator. This is due to the fact that, as a payor, Medicare generally will only cover IVDs that have passed FDA premarket review—either approval or clearance—where such FDA review is required by applicable statute and regulation.[21] However, in these cases, FDA approval or clearance is not sufficient in and of itself to result in a favorable coverage decision by CMS for any given IVD.[22]

Definitions[23]

In Vitro Diagnostic (IVD) Device: Device used in the analysis of human samples; includes commercial test products and instruments used in testing, among other things.

Laboratory-Developed Test (LDT): A class of IVD that is manufactured, including being developed and validated, and offered, within a single laboratory. LDTs may sometimes be referred to as "home-brew tests." (Source: FDA. [2010] Oversight of Laboratory Developed Tests; Public Meeting; Request for Comments; F.R. 2010-14654. http://www.gpo.gov/fdsys/pkg/FR-2010-06-17/html/2010-14654.htm.)

All LDTs are IVDs.

Genetic Test: A test that analyzes various aspects of an individual's genetic material (DNA, RNA, chromosomes, and genes).

All genetic tests are IVDs. Most genetic tests are LDTs.

This report provides an overview of federal regulation of IVDs by FDA, through the Federal Food, Drug, and Cosmetics Act (FFDCA) and the Public Health Service Act (PHSA), and by CMS, through the Clinical Laboratory Improvement Amendments (CLIA) of 1988.[24] It then provides a discussion of the oversight of LDTs—including the history of the debate over regulating LDTs and a description of FDA's recently announced *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*—as well as an overview of the regulation of DTC genetic tests. Terms used throughout this report are defined in the text box.

(...continued)

non-physician practitioner who is treating the patient." See CMS, "Clinical Laboratory Fee Schedule: Payment System Fact Sheet Series," January 2012, http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/downloads/clinical_lab_fee_schedule_fact_sheet.pdf.

[20] For more information about payment under Medicare for clinical diagnostic laboratory services, see CRS Report RL30526, *Medicare Payment Updates and Payment Rates*, coordinated by (name redacted).

[21] For novel and high-risk devices, premarket review entails conducting clinical studies, submitting the results of the clinical studies along with a premarket approval (PMA) application, and requires evidence providing reasonable assurance that the device is safe and effective. The PMA process results in a type of FDA permission called *approval*. For moderate-risk devices, premarket review involves submitting a 510(k) notification demonstrating that the device is substantially equivalent to a device already on the market (a predicate device) that does not require a PMA. The 510(k) process, named for its authorizing FFDCA section, is unique to medical devices and results in FDA *clearance*. Substantial equivalence is determined by comparing the performance characteristics of a new device with those of a predicate device; clinical data demonstrating safety and effectiveness are usually not required.

[22] For further details, see the Secretary's Advisory Committee on Genetics, Health, and Society, 2006, "Coverage and Reimbursement of Genetic Tests and Services;" p. 29, http://oba.od.nih.gov/oba/sacghs/reports/CR_report.pdf.

[23] For the purposes of this report, the definitions include only those tests that are health-related.

[24] P.L. 100-578, PHSA §353. All clinical laboratories that perform testing on a human specimen for health related purposes are regulated under the authority of CLIA, regardless of whether they participate in either or both the Medicare and Medicaid programs.

FDA Regulation of IVD Devices[25]

As with other medical devices, the application of FDA regulatory requirements to IVDs depends on the IVD's risk classification according to its intended use. Risk classification "is based on the risk the device poses to the patient or the user and the information available to address that risk."[26] The risk classification process is described in more detail in the "IVD Regulatory Requirements" section of this report. IVDs are defined in regulation as a specific subset of medical devices that include "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions ... in order to cure, mitigate, treat, or prevent disease ... [s]uch products are intended for use in the collection, preparation, and examination of specimens taken from the human body."[27]

As indicated by this definition, an IVD may be either a complete test or a component of a test. In either case, the IVD comes under FDA's regulatory purview. Test components include both non-diagnostic ingredients, called general purpose reagents (GPRs),[28] and the active ingredient in a diagnostic test, referred to as the analyte specific reagent (ASR).[29]

There are two routes to market for an IVD used in the clinical management of patients. In one route, the product is developed, produced, and sold by a manufacturer for distribution to multiple laboratories—referred to as a "commercial test kit." In the second route, the product is developed by and used in a single laboratory—referred to as a "laboratory developed test," or LDT. LDTs may use ASRs or GPRs that are either manufactured in-house by the laboratory or that are commercially developed and distributed. The FDA has been generally exercising enforcement discretion for LDTs in that the agency has generally not enforced applicable regulatory requirements.

FDA's Authority to Regulate In Vitro Diagnostic (IVD) Devices

IVDs that are used in the clinical management of patients generally fall under the definition of medical device and therefore are subject to regulation by the FDA. The FDA derives its authority to regulate the sale and distribution of medical devices from the Medical Device Amendments of 1976 (MDA, P.L. 94-295), which amended the FFDCA. Congress via the MDA amended the definition of "device" and outlined a basic process for premarket approval and clearance of such devices, among other things.

---

[25] For further information about FDA regulation of medical devices broadly, see CRS Report R42130, *FDA Regulation of Medical Devices*, by (name redacted).

[26] Elizabeth Mansfield, Timothy J. O'Leary, and Steven I. Gutman, "Food and Drug Administration Regulation of *in Vitro* Diagnostic Devices," *Journal of Molecular Diagnostics*, vol. 7, no. 1 (February 2005), pp. 2-7.

[27] 21 C.F.R. §809.3(a); Definitions.

[28] A GPR is "a chemical reagent that has general laboratory application, is used to collect, prepare, and examine specimens from the human body for diagnostic purposes, and is not labeled or otherwise intended for a specific diagnostic application ... [GPRs] do not include laboratory machinery, automated or powered systems." 21 C.F.R. §864.4010(a).

[29] An analyte is defined as a substance or chemical constituent undergoing analysis. ASRs are "antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens." 21 C.F.R. §864.4020(a).

The term "device" is statutorily defined as "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro reagent*, or other similar or related article, including any component, part, or accessory" (emphasis added) that is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or is intended to affect the structure or any function of the body of man or other animals."[30] Some tests may be used for non-health related purposes; for example, certain genetic testing may be used to determine ancestry. It has been noted that this type of test would not come under the FDA's regulatory purview.[31]

In some limited cases, IVDs may fall under the statutory definition of a biological product, and are therefore subject to the requirements of the PHSA for the licensure of biological products.[32] Such IVDs include, for example, blood donor screening tests for infectious agents (HIV, hepatitis B and C), blood grouping, and cross-matching prior to transfusion.[33] Given that IVDs may fall under either the definition of medical device or biological product, they are regulated by FDA primarily through the Center for Devices and Radiological Health (CDRH) and additionally by the Center for Biologics Evaluation and Research (CBER).[34]

IVD Regulatory Requirements

FDA uses a risk-based regulatory scheme for medical devices, including IVDs. IVDs receive their risk classification based on their intended use and the risk relative to that use. The intended use "is established according to the claims the manufacturer or sponsor intends to make for the device, and includes the target population and the clinical setting for the use of an IVD."[35] In addition, classification is based on the risk the device poses to the patient; for IVDs this is the risk to the patient of an incorrect test result. Congress provided definitions in the MDA for the three device classes—class I, class II, class III—based on the level of risk; low-, moderate-, and high-risk, respectively. About 50% of IVDs are class I, 42% are class II and 8% are class III.[36] Device classification determines the type of premarket regulatory requirements that a manufacturer must follow.

[30] FFDCA §201(h).

[31] See, for example, JK Wagner et al., "Tilting at windmills no longer: A data-driven discussion of DTC DNA ancestry testing," *Genetics in Medicine,* vol. 14, no.6 (2012), pp. 586-593.

[32] PHSA §351; Regulation of Biological Products.

[33] FDA, CDRH/CBER, *Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies—Frequently Asked Questions*, Rockville, MD, June 25, 2010, p. 5, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071230.pdf.

[34] Ibid., pp. 6-7. Within CDRH, IVD products are reviewed by the Office of In Vitro Diagnostics and Radiological Health (OIR), formerly called the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD). http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm115904.htm.

[35] Zivana Tezak, Marina V. Kondratovich, and Elizabeth Mansfield, "US FDA and personalized medicine: in vitro diagnostic regulatory perspective," *Personalized Medicine*, vol. 7, no. 5 (2010), pp. 517-530.

[36] FDA/CDRH Public Meeting: Oversight of Laboratory Developed Tests (LDTs), July 19, 2010, transcript, p. 45. http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM226203.pdf.

Many low-risk devices (class I) are exempt from premarket review through the respective classification regulations and manufacturers need not submit an application to FDA prior to marketing.[37] Premarket review is required for moderate- and high-risk devices (class II and class III).[38] In general, there are two main pathways that manufacturers can use to bring such devices to market. One pathway consists of conducting clinical studies and submitting a premarket approval (PMA) application, which requires evidence providing reasonable assurance that the device is safe and effective. The PMA process is generally used for novel and high-risk devices and results in a type of FDA permission called *approval*. The other path involves submitting a 510(k) notification demonstrating that the device is substantially equivalent to a device already on the market—a predicate device—that does not require a PMA.[39] The 510(k) process is unique to medical devices and, if successful, results in FDA *clearance*. Substantial equivalence is determined by comparing the performance characteristics of a new device with those of a predicate device; clinical data demonstrating safety and effectiveness are usually not required. The FDA has 180 days to review a PMA application and 90 days to review a 510(k) notification. Once a PMA application is approved or a 510(k) notification is cleared for marketing, manufacturers must comply with regulations on manufacturing, labeling, surveillance, device tracking, and adverse event reporting.[40] In addition, any future modification of the device must be cleared or approved by the FDA.

General Controls

General controls include both pre- and postmarket requirements, and are the minimum regulations that apply to all FDA regulated medical devices. Among other things, general controls include the following:

1. Establishment Registration
2. Device Listing
3. Good Manufacturing Practices
4. Labeling
5. Premarket Notification

Source: See FDA, *General Controls for Medical Devices*, May 13, 2009, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm055910.htm Accessed July 30, 2013.

Class I devices are those under current law for which general controls "are sufficient to provide reasonable assurance of the safety and effectiveness of the device."[41] This is the lowest risk category; most class I devices are exempt from premarket review though they still have to comply with the other general controls (see text box). "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.... 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."[42]

Class II devices are those under current law "which cannot be classified as class I because the general controls by themselves are insufficient to provide reasonable assurance of safety and

[37] FFDCA §513(a)(1)(A).

[38] FFDCA §513(a)(1)(B) and (C).

[39] For novel low-to-moderate risk devices without a predicate, there is an alternative called the de novo process; FFDCA §513(f).

[40] For example, specific requirements on IVD device labeling are found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/InVitroDiagnosticDeviceLabelingRequirements/default.htm.

[41] FFDCA §513(a)(1)(A).

[42] Shuren, *Direct-to-Consumer Genetic Testing*, testimony on July 22, 2010.

effectiveness of the device."[43] Class II includes devices that pose a moderate risk to patients and are typically subject to general controls and special controls. It 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."[44] Special controls may include special labeling requirements, mandatory performance standards, and postmarket surveillance.

Class III is the highest risk category. Under current law, general and special controls are not sufficient to ensure safe and effective use of a class III device which therefore is subject to premarket approval—PMA—requirements.[45] Class III "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."[46] The PMA application must provide "valid scientific evidence" which usually requires clinical studies.[47]

In most cases, a clinical evaluation of an investigational device must have an investigational device exemption (IDE) before a clinical study is initiated.[48] An IDE allows an unapproved or uncleared device to be used in a clinical study to collect the data required to support a premarket submission.[49] The IDE permits a device to be shipped lawfully for investigation of the device without requiring that the manufacturer comply with other requirements of the FFDCA, such as registration and listing. Many IVD devices would be exempt from IDE requirements if, for example, testing is noninvasive, does not require invasive sampling, does not introduce energy into a subject, and does not stand alone (i.e., is not used for diagnosis without confirmation by other methods or medically established procedures).[50] However, even if a particular IVD study is exempt from most IDE requirements, it still would be subject to other requirements, such as informed consent of study subjects.[51]

Commercial Test Kits vs. Laboratory Developed Tests (LDTs)

FDA has historically focused its oversight of IVDs on diagnostic test kits that have been broadly marketed to laboratories or the public. Examples include tests for infectious disease, blood

[43] FFDCA §513(a)(1)(B).

[44] Shuren, *Direct-to-Consumer Genetic Testing*, testimony on July 22, 2010.

[45] FFDCA §513(a)(1)(C).

[46] Shuren, *Direct-to-Consumer Genetic Testing*, testimony on July 22, 2010.

[47] FFDCA §513(a)(3)(B) and (a)(3)(D).

[48] See 21 C.F.R. §812. An investigational device is defined as "a device, including a transitional device, that is the object of an investigation." 21 C.F.R. §812.3.

[49] FDA, Device Advice: Investigational Device Exemption (IDE), July 9, 2009, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm.

[50] See 21 C.F.R. §812.2(c)(3). Further details are provided in FDA, CDRH/CBER, Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies—Frequently Asked Questions, Rockville, MD, June 25, 2010, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071230.pdf

[51] 21 C.F.R. §50 (Informed Consent), 21 C.F.R. §56 (Institutional Review Board), 21 C.F.R. §812.119 (Disqualification of a Clinical Investigator).

glucose tests, and pregnancy tests. In contrast, laboratory developed tests (LDTs)—a subset of IVDs—may be defined as "a class of in vitro diagnostics that are manufactured, including being developed and validated, and offered, within a single laboratory."[52] LDTs are often used to test for conditions or diseases that are either rapidly changing (e.g., new infectious diseases or new strains of known infectious diseases) or for those that are the subject of quickly advancing scientific research (e.g., genomic testing for cancer). LDTs have not traditionally been regulated by FDA; this issue is discussed later in the report (see "History of the Regulation of LDTs").

Analyte Specific Reagents (ASRs)

FDA is generally enforcing applicable regulatory requirements for components of IVDs even if the agency is exercising enforcement discretion for the complete test. Analyte specific reagents (ASRs), a component of tests, have a particular diagnostic use and therefore are regulated as class I, II, or III depending on their application's level of risk. An ASR is defined as "antibodies, ... specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens."[53] For example, ASRs used for diagnosis of human immunodeficiency virus (HIV) or other contagious and fatal diseases must meet class III requirements because of the high risk posed by a test malfunction.

General Purpose Reagents (GPRs)

A general purpose reagent (GPR) is defined as "a chemical reagent that has general laboratory application, that is used to collect, prepare, and examine specimens from the human body for diagnostic purposes, and that is not labeled or otherwise intended for a specific diagnostic application."[54] Examples of GPRs include buffer solutions and some enzymes. General purpose reagents are usually regulated as class I devices and are exempt from the premarket 510(k) notification procedures.

IVD Products for Research Use Only (RUO) or Investigational Use Only (IUO)

In November 2013, FDA issued guidance on the use of IVD products labeled for "Research Use Only" (RUO) or for "Investigational Use Only" (IUO).[55] Such IVD products include reagents, instruments, and systems that have not been approved, cleared, or licensed by FDA. "The term RUO refers to devices that are in the laboratory phase of development. The term IUO refers to devices that are in the product testing phase of development."[56] IUO products may be used in research testing on human samples and the research may eventually lead to the clearance, approval, or licensure of a new IVD for clinical diagnostic use. The manufacturer of such an

[52] FDA, "Oversight of Laboratory Developed Tests; Public Meeting; Request for Comments," 75 *Federal Register*, 14654, June 17, 2010, http://www.gpo.gov/fdsys/pkg/FR-2010-06-17/html/2010-14654.htm.

[53] 21 C.F.R. §864.4020; Analyte Specific Reagents.

[54] 21 C.F.R. §864.4010; General purpose reagent.

[55] FDA, CDRH/CBER, *Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only*, Guidance, November 25, 2013, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM376118.pdf.

[56] Ibid., p. 7.

RUO or IUO IVD product may legally sell it—without FDA premarket review—as long as the product is only for research or investigational use and not for clinical diagnostic use.

FDA has expressed its concern that the "distribution of unapproved and uncleared IVD products labeled RUO or IUO, but intended for purposes other than research or investigation (for example, for clinical diagnostic use), has led, in some cases, to the clinical diagnostic use of products with unproven performance characteristics, and with manufacturing controls that are inadequate to ensure consistent manufacturing of the finished product. Use of such tests for clinical diagnostic purposes may mislead healthcare providers and cause serious adverse health consequences to patients, who are not aware that they are being diagnosed with research or investigational products."[57] The purpose of the FDA 2013 guidance is to "clarify the requirements applicable to RUO and IUO IVD products, including that RUO and IUO labeling must be consistent with the manufacturer's intended use of the device."[58]

IVD Companion Diagnostic Devices (CoDx)

FDA defines an IVD companion diagnostic (CoDx) device as "an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product."[59] According to FDA, this definition excludes tests that are not a determining factor in the safe and effective use of the therapeutic product. CoDx tests "identify patients who are most likely to benefit from a particular therapeutic product" or are "likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product."[60] The instructions for use labeling of the therapeutic product would stipulate the use of the IVD companion diagnostic device.

One of the earliest examples of the co-development of a drug and diagnostic was the FDA approval in 1998 of a CoDx along with Herceptin as a treatment for breast cancer. "[C]linicians now commonly use diagnostics to determine which breast tumors overexpress the human epidermal growth factor receptor type 2 (HER2), which is associated with a worse prognosis but also predicts a better response to the medication trastuzumab [Herceptin]. A test for HER2 was approved along with the drug (as a "companion diagnostic") so that clinicians can better target patients' treatment."[61] Another reason for the combined approval is that use of the CoDx can avoid the toxic side effects to the heart caused by Herceptin in those who would not benefit from the drug.[62]

Other examples of FDA-approved drugs and companion diagnostics include Erbitux used to treat metastatic colorectal cancer; Gleevec for gastrointestinal stromal tumors; Zelboraf for late-stage melanoma; Xalkori for late-stage lung cancer; Tarceva for non-small cell lung cancers; and

[57] Ibid., pp. 4-5.

[58] Ibid., p. 5.

[59] FDA, Draft Guidance for Industry and Food and Drug Administration Staff, "In Vitro Companion Diagnostic Devices," July 14, 2011, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm.

[60] Ibid.

[61] Hamburg, "Path to Personalized Medicine," pp. 301-304.

[62] Institute of Medicine, "Refining Processes for the Co-Development of Genome-Based Therapeutics and Companion Diagnostic Tests: Workshop Summary," 2014, p. 8. IOM held a workshop in February 2013 on the "co-development of targeted therapeutics and companion molecular tests for prediction of drug response."

Tafinlar and Mekinist for advanced melanoma.[63] FDA expects that many companion diagnostic devices will be class III "owing to the likelihood of harm to the patient if the diagnostic result is incorrect."[64]

Clinical Laboratory Improvement Amendments of 1988 (CLIA)

Oversight of IVDs: The Role of CMS and FDA

CMS: CMS regulates clinical laboratories that carry out diagnostic testing through the authority of the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

FDA: The FDA regulates the distribution in interstate commerce of IVDs and their components under the authority of the FFDCA.

Source: Mansfield, "FDA Regulation of in Vitro Diagnostic Devices."

The Clinical Laboratory Improvement Amendments (CLIA) of 1988 provides CMS with authority to regulate clinical laboratories.[65] CLIA establishes quality standards for clinical laboratory testing and a certification program for clinical laboratories that perform testing using IVD devices. All laboratories that perform diagnostic testing for health-related reasons (i.e., with results returned to the patient or a health care practitioner) are regulated by CMS under the authority of CLIA. For CLIA to apply, testing must be carried out on a human specimen.

The FDA pursuant to the FFDCA, and CMS through CLIA, have different regulatory goals. FDA regulation "addresses the safety and effectiveness of the diagnostic tests themselves and the quality of the design and manufacture of the diagnostic tests."[66] CLIA regulates the quality of the clinical testing process itself, mostly by assessing the quality of the clinical laboratory. However, this oversight also includes requirements that assess the performance of the tests themselves and, therefore, there is some overlap in the two agencies' approaches. Specifically, CLIA requirements evaluate a test's *analytical validity*, whereas the FDA's premarket review requirements assess a test's *analytical validity and clinical validity*. Analytical validity is defined as the ability of a test to detect or measure the analyte it is intended to detect or measure; the clinical validity of a test is defined as its ability to accurately diagnose or predict the risk of a particular clinical outcome.[67] To summarize, FDA oversight of IVDs—and not CLIA oversight—includes the following components: (1) the regulation of the safety and effectiveness of the test; (2) pre-market review of the test; (3) demonstration of clinical validity; (4) systematic adverse event reporting; and (5) a process for corrections or recalls.[68]

[63] Hamburg, "Path to Personalized Medicine," p. 303; FDA Commissioner's Address, Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 2, 2013, http://www.fda.gov/NewsEvents/Speeches/ucm354888.htm; and, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.

[64] Tezak, "US FDA and personalized medicine," p. 519.

[65] PHSA §353.

[66] Shuren, *Direct-to-Consumer Genetic Testing*, testimony on July 22, 2010.

[67] For more information about analytical and clinical validity specifically in the context of genetic testing, see CRS Report RL33832, *Genetic Testing: Scientific Background for Policymakers*, by (name redacted).

[68] Testimony of AdvaMedDx Executive Director Andrew Fish, in U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health, *21st Century Cures: Examining the Regulation of Laboratory-Developed Tests,* hearings, 113th Cong., 2nd sess., September 9, 2014, p. 3.

In 1988, Congress passed CLIA in response to concern about the quality of clinical laboratory testing, and specifically, concerns about Pap smears. This law expanded the Department of Health and Human Services' (HHS's) existing authority to regulate clinical laboratories (and therefore clinical laboratory testing) to include any clinical laboratory that examines "materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings."[69] All such facilities are required to receive certification demonstrating that they meet certain requirements,[70] as well as specific quality standards "to assure consistent performance by laboratories issued a certificate … of valid and reliable laboratory examinations and other procedures."[71] CLIA does not apply to laboratories conducting only tests for research purposes, or to laboratories in those states where state law establishes requirements of equal or greater stringency (currently, these states are New York and Washington).

CLIA certification is based on the level of complexity of testing that the laboratory performs, specifically (1) low (therefore, waived) complexity; (2) moderate complexity; and (3) high complexity. The FDA has responsibility for categorizing tests according to their level of complexity.[72] This FDA role is distinct from the device risk classification discussed in the "IVD Regulatory Requirements" section of this report. Laboratories that perform moderate and high complexity testing must meet specific standards and requirements as a condition of certification, including proficiency testing (PT), patient test management, quality control, personnel qualifications, and quality assurance. An inspection is part of the initial certification process, and CMS (or another survey and certification entity) may perform subsequent inspections on a biennial basis to ensure continued compliance with the requirements of CLIA.[73] Laboratories that only perform waived tests receive a certificate of waiver (COW) from CMS; under current law, waived tests are those "that have been approved by the FDA for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result."[74]

In order to monitor the quality, accuracy, and reliability of testing carried out by CLIA-certified laboratories (those conducting moderate and high complexity testing, as noted above), CMS requires the laboratory to carry out proficiency testing. Proficiency testing is defined as, "the testing of unknown samples sent to a laboratory by a CMS-approved proficiency testing program"[75] and is required and defined in regulation for certain specialties and subspecialties (e.g., virology, chemistry, endocrinology). Laboratories carrying out moderate or high complexity testing must be certified in each specialty or subspecialty in which they carry out such testing.

Proficiency test samples must be tested in the same way that the laboratory tests its patient samples, and sent back to the approved proficiency testing program for analysis. In this way, the quality of the laboratory's services may be evaluated. Given the role of proficiency testing in the certification process, CLIA prohibits laboratories from sending the samples they receive for

[69] PHSA §353(a), "Definitions."

[70] PHSA §353(d), "Requirements for Certification."

[71] PHSA §353(f), "Standards."

[72] See FDA, "CLIA Categorization Criteria," http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124208.htm.

[73] 42 CFR §493.1777, Subpart Q.

[74] PHSA §353(d)(3), "Requirements for Certificate of Waiver."

[75] CMS, "CLIA: Proficiency Testing," p. 2, https://www.cms.gov/CLIA/downloads/CLIAbrochure8.pdf.

proficiency testing out to another laboratory for processing. Additionally, as a condition of certification, a laboratory must agree "to treat proficiency testing samples in the same manner as it treats materials derived from the human body referred to it for laboratory examinations or other procedures in the ordinary course of business."[76]

All LDTs, including genetic tests offered as LDTs, are considered high complexity tests under CLIA and therefore labs conducting these tests would otherwise have to carry out proficiency testing. However, in practice, there are no specified proficiency testing requirements for genetic testing laboratories, because genetics is not a designated specialty area and none of the specified regulated analytes include nucleic acids (RNA, DNA).[77] Some labs that conduct genetic testing are also conducting moderate or high complexity testing in other specialty or subspecialty areas that do have specified proficiency testing requirements. The Centers for Disease Control and Prevention's (CDC) Clinical Laboratory Improvement Advisory Committee (CLIAC) recommended adding a genetic specialty under CLIA, and CMS considered but eventually decided against such an action.[78] This decision was made partially based on a potential lack of sufficient proficiency testing samples for many genetic tests and the absence of a mechanism for assessing clinical validity due to lack of adequate data.[79]

Oversight of Laboratory Developed Tests (LDTs)

FDA has, to date, focused its enforcement efforts on commercial IVDs, which are broadly marketed to labs or to the public, and has not generally enforced the pre-market clearance or approval requirements for LDTs. In recent years, however, FDA has indicated its intent to broadly regulate LDTs using a risk-based approach. On July 31, 2014, the agency officially notified Congress[80] of its intent to do so in fulfillment of a statutory requirement in the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA, P.L. 112-144). On September 30, 2014, the agency posted draft guidance on its website, and on October 3, 2014, the agency published a notice in the *Federal Register* announcing the availability of the guidance documents and the start of a 120-day comment period.[81]

The agency's steps to regulate LDTs have drawn support from those concerned about device safety, and criticism from some who are concerned about the scope of FDA's statutory authority over LDTs as well as the potential impact of regulation on innovation. It has also attracted the

[76] PHSA §353(d)(1)(E), "Requirements for Certificates."

[77] 42 CFR §493, Subpart I, "Proficiency Testing Programs for Nonwaived Testing."

[78] CLIAC provides advice and guidance to HHS on improving clinical laboratory quality and laboratory medicine practice. http://wwwn.cdc.gov/CLIAC/About.aspx.

[79] SACGHS, "U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services," April 2008, http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf.

[80] Food and Drug Administration, "FDA takes steps to help ensure the reliability of certain diagnostic tests," July 31, 2014, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm407321.htm. The notification to Congress consists of two guidance documents, "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)," discussed above, and "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)." http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407409.pdf.

[81] FDA, "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs); Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Availability," October 3, 2014, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf. 79 Fed. Reg. 59776, October 3, 2014.

attention of Congress; for example, on September 9, 2014, the House Committee on Energy and Commerce, Subcommittee on Health, held a hearing on the topic of FDA's notice that it will enforce regulatory requirements for LDTs.[82] The House Committee on Energy and Commerce also released a white paper on December 9, 2014, soliciting comments on a series of specific questions relating to the regulation of LDTs and IVD commercial test kits.[83]

In response to the draft guidance, the American Clinical Laboratory Association (ACLA) announced that it has retained counsel with expertise in constitutional law and administrative procedure to represent the association in matters relating to the guidance. In a press release, ACLA states its position that LDTs "are not commercially distributed products … they are an integral part of the physician's practice of medicine. Thus, [the Association] continues to believe that LDTs are not medical devices and that the FDA does not have the statutory authority to regulate them as devices."[84]

History of the Regulation of LDTs

Generally, the FDA has maintained that it has clear regulatory authority over LDTs, as it does with all IVDs that meet the definition of medical device in the FFDCA.[85] However, despite this, the FDA traditionally exercised enforcement discretion over LDTs, choosing not to enforce applicable regulations with respect to such tests.[86] Beginning in 1997, several governmental entities "questioned the appropriateness of the FDA's policy of enforcement discretion toward LDTs, including the National Institutes of Health (NIH) and Department of Energy's Joint Task Force on Genetic Testing, the Secretary's Advisory Committee on Genetic Testing (SACGT), and the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS)."[87,88] More recently, "other groups have pointed out the lack of effective oversight and made specific

[82] U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health, hearing on *21st Century Cures: Examining the Regulation of Laboratory Developed Tests,*113th Cong., 2nd sess., September 9, 2014.

[83] U.S. Congress, House Committee on Energy and Commerce, "21st Century Cures—Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests," December 9, 2014, http://energycommerce.house.gov/press-release/21st-century-cures-solicits-feedback-regulation-vitro-diagnostic-test-kits-and.

[84] ACLA, "ACLA Retains Attorneys Paul D. Clement and Laurence H. Tribe To Represent ACLA in Opposing the FDA's Proposal To Treat Laboratory Developed Tests (LDTs) as Medical Devices," November 18, 2014, http://www.acla.com/acla-retains-attorneys-paul-d-clement-and-laurence-h-tribe-to-represent-acla-in-opposing-the-fdas-proposal-to-treat-laboratory-developed-tests-ldts-as-medical-devices/.

[85] Shuren, *Direct-to-Consumer Genetic Testing*, testimony on July 22, 2010.

[86] FDA, "Oversight of Laboratory Developed Tests; Public Meeting; Request for Comments;" 75 *Federal Register*, 14654, June 17, 2010, http://www.gpo.gov/fdsys/pkg/FR-2010-06-17/html/2010-14654.htm.

[87] Tezak, "US FDA and personalized medicine," p. 525.

[88] A July 2000 report by SACGT recommended that "FDA should be the federal agency responsible for the review, approval, and labeling of all new genetic tests that have moved beyond the basic research phase." SACGT was chartered in 1998 "to advise the Department of Health and Human Services (DHHS) on the medical, scientific, ethical, legal, and social issues raised by the development and use of genetic tests." Following expiration in August 2002 of SACGT's charter, SACGHS was chartered in 2002 as "a public forum for deliberation on the broad range of policy issues raised by the development and use of genetic tests and, as warranted, to provide advice on these issues." In an April 2008 report on the oversight of genetic tests, SACGHS recommended that FDA "should address all laboratory tests in a manner that takes advantage of its current experience in evaluating laboratory tests." See Department of Health and Human Services, Secretary's Advisory Committee on Genetics, Health, and Society, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, Washington, DC, April 2008, http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf.

recommendations regarding the regulation of LDTs."[89] Examples include the pharmaceutical manufacturer Genentech, the Advanced Medical Technology Association (AdvaMed), and the College of American Pathologists (CAP).[90] On the other hand, some representatives of clinical laboratories and manufacturers of LDTs, such as the American Clinical Laboratory Association (ACLA), have asserted that LDTs should be outside of the FDA's regulatory purview.[91] To clarify the distinction between an LDT and an in vitro commercial test kit, the Association for Molecular Pathology (AMP) has proposed a new name for LDTs: laboratory-developed procedures (LDPs), defined as "a professional service that encompasses and integrates the design, validation, verification, and quality systems used in laboratory testing and interpretative reporting in the context of clinical care."[92]

In 2006, FDA published draft guidance on a specific subset of LDTs called In Vitro Diagnostic Multivariate Index Assays (IVDMIAs).[93] IVDMIAs are defined by the FDA as tests that, among other things, provide results that are not transparent and that the end user (usually a physician) could not independently derive.[94] The draft guidance announced that "the enforcement discretion for tests meeting the definition of an IVDMIA would be terminated"; it attracted "both intense criticism and strong support."[95] In a second draft guidance, published in 2007, the FDA states:

> IVDMIAs raise significant issues of safety and effectiveness. These types of tests are developed based on observed correlations between multivariate data and clinical outcome, such that the clinical validity of the claims is not transparent to patients, laboratorians, and clinicians who order these tests. Additionally, IVDMIAs frequently have a high risk intended use. FDA is concerned that patients are relying upon IVDMIAs with high risk intended uses to make critical healthcare decisions when FDA has not ensured that the IVDMIA has been clinically validated and the healthcare practitioners are unable to clinically validate the test themselves. Therefore, there is a need for FDA to regulate these devices to ensure that the IVDMIA is safe and effective for its intended use.[96]

The FDA never finalized its guidance concerning IVDMIAs, and instead announced its intent to regulate all LDTs.[97] In June 2010, FDA announced it would hold a public meeting the following

[89] Tezak, "US FDA and personalized medicine," p. 526.

[90] Ibid.

[91] Testimony of The American Clinical Laboratory Association (ACLA) President Alan Mertz, in U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health, *21st Century Cures: Examining the Regulation of Laboratory-Developed Tests,* hearings, 113th Cong., 2nd sess., September 9, 2014, http://docs.house.gov/meetings/IF/IF14/20140909/102625/HHRG-113-IF14-Wstate-MertzA-20140909.pdf.

[92] Andrea Ferreira-Gonzalez et al., "Revisiting Oversight and Regulation of Molecular-Based Laboratory-Developed Tests," *The Journal of Molecular Diagnostics*, vol.16, no. 1 (January 2014).

[93] Ibid., p. 527.

[94] FDA's 2007 draft guidance defined IVDMIA as "a device that 1) combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a "classification," "score," "index," etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and 2) provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user." FDA, *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff - In Vitro Diagnostic Multivariate Index Assays*, July 26, 2007, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm.

[95] Tezak, "US FDA and personalized medicine," p. 527.

[96] FDA, *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff - In Vitro Diagnostic Multivariate Index Assays*, July 26, 2007, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm.

[97] 75 *Federal Register* 34462, June 17, 2010.

month to allow stakeholders the opportunity to discuss the agency's decision to exercise its regulatory authority over all LDTs.[98] FDA presentations during that July 2010 public meeting provided a number of reasons for its decision to assert its enforcement authority over all LDTs, including the following:

- The volume and types of LDTs have grown considerably, with a high proportion of these tests developed in commercial laboratories or biotechnology companies.
- LDTs have evolved to be more like commercial in vitro devices. LDTs are no longer tests developed in a laboratory for patients in a regional medical setting with consultation occurring between the pathologist and the ordering physician.
- The LDT route to market is viewed as a favorable business model and driving venture capital funding for clinical diagnostics. Companies see the laboratory developed testing pathway as an easier route to market to avoid FDA regulation of their tests. In addition, manufacturers who develop commercial test kits, which are required to go through FDA premarket review, may be at a competitive disadvantage with LDT manufacturers.
- Some LDTs are aggressively marketed directly to clinicians via Internet sales.
- The public needs assurances that LDTs are sound and reliable. FDA asserted that at the present time, "diagnostics critical for patient care may not be developed in a manner that provides a reasonable assurance of safety and effectiveness."[99]

Some clinical laboratories and manufacturers of LDTs have asserted that LDTs should be outside of the FDA's regulatory purview. On June 4, 2013, the American Clinical Laboratory Association (ACLA) filed a citizen petition under the FFDCA requesting that the agency "refrain from issuing draft or final guidance or a proposed or final rule purporting to regulate LDTs as devices."[100] ACLA states that FDA lacks statutory authority to regulate LDTs because ACLA claims that LDTs are not devices as defined under the FFDCA. ACLA maintains that LDTs are "proprietary procedures" and therefore not subject to regulation under the FFDCA. In addition, ACLA asserts that LDTs do not meet the FDA definition of "commercial distribution" which requires "that a product be delivered, distributed, or placed on the market."[101]

In a June 2013 speech, FDA Commissioner Margaret A. Hamburg stated that the agency had under development a "risk-based framework" for the regulation of LDTs.[102] Section 1143 of

[98] 75 *Federal Register* 34462 June 17, 2010.

[99] 75 *Federal Register* 34462, June 17, 2010. Gail H. Vance, "College of American Pathologists Proposal for the Oversight of Laboratory-Developed Tests," *Archives of Pathology Laboratory Medicine,* vol. 135, (November 2011), pp.1432-1435, based on FDA presentations by Courtney Harper and Elizabeth Mansfield at the July 2010 meeting, http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM226203.pdf.

[100] Citizen Petition, American Clinical Laboratory Association, June 4, 2013, http://www.acla.com/sites/default/files/ACLA%20Citizen%20Petition%20re%20LDTs.pdf.

Other citizen petitions "advocating against FDA regulation of LDTs" were filed in 1992 by Hyman, Phelps and McNamara, and in 2006 by the Washington Legal Foundation. FDA Law Blog, June 5, 2013, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/06/fda-commissioner-calls-for-more-active-fda-regulation-of-laboratory-developed-tests-and-acla-promptl.html.

[101] Citizen Petition, American Clinical Laboratory Association, June 4, 2013, pp. 2-3, http://www.acla.com/sites/default/files/ACLA%20Citizen%20Petition%20re%20LDTs.pdf.

[102] Food and Drug Administration, Commissioner's Address, Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 2, 2013, http://www.fda.gov/NewsEvents/Speeches/ucm354888.htm.

FDASIA stipulates that the agency "may not issue any draft or final guidance on the regulation" of LDTs without, "at least 60 days prior to such issuance," first notifying Congress "of the anticipated details of such action."[103] On July 31, 2014, in fulfillment of this statutory requirement, the FDA officially notified Congress that it would be issuing draft guidance,[104] and on October 3, 2014, the agency published a notice in the *Federal Register* announcing the availability of the guidance documents and requesting comments within 120 days to ensure their consideration in the development of final guidance.

FDA's Draft Guidance: "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)"

In its draft guidance, "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)," the FDA presents the details of a risk-based framework for regulating LDTs. The framework generally identifies classes of LDTs that will be (1) exempt from regulation entirely; (2) only required to meet registration and listing (or notification) and adverse event reporting requirements; and (3) required to meet registration and listing (or notification), adverse event reporting, applicable premarket review (PMA or 510(k) notification), and quality system regulation requirements.[105] The determination to continue enforcement discretion—or to enforce certain or all applicable regulatory requirements—for an LDT will be based on risk evaluation.

This framework relies on the following definition of LDT: "[An LDT is] an IVD that is intended for clinical use and [is] designed, manufactured and used within a single laboratory."[106] FDA notes that there are numerous examples of tests that do not meet this strict definition of an LDT that are nevertheless being marketed as LDTs; in these cases, the LDT regulation will apply to these tests in an effort to maintain continuity in the market. Examples of tests that are being marketed as LDTs, but that do not meet the FDA's narrow definition of LDT, include (1) tests that include a key component manufactured by a third party under contract to the clinical laboratory that makes the tests; and (2) tests that were transferred to multiple clinical laboratories that are under ownership of a single entity that developed the tests.[107]

[103] Food and Drug Administration Safety and Innovation Act (FDASIA, P.L. 112-144), §1143; this provision sunsets in July 2017.

[104] Food and Drug Administration, "FDA takes steps to help ensure the reliability of certain diagnostic tests," July 31, 2014, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm407321.htm. The notification to Congress consists of two guidance documents: "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)," discussed above, and "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)." http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407409.pdf.

[105] FDA states, on pages 8-9 of the framework guidance document, that adverse event reports for LDTs are required under the manufacturer medical device reporting requirements (21 CFR 803.50), but due to the policy of enforcement discretion for LDTs, such reports "have not been systematically reported or collected." The framework document uses the terms "adverse event reporting" and "medical device reporting" interchangeably (see p. 14 of the framework).

[106] Food and Drug Administration, *Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories*, Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs), July 31, 2014, p. 4.

[107] Ibid.

Two subsets of LDTs will not fall under the purview of the LDT regulatory framework. FDA will exercise full enforcement discretion over: LDTs used solely for forensic purposes, and LDTs used for organ, stem cell and tissue transplantation.[108]

For all remaining LDTs, FDA will use the information obtained through the registration and listing (or notification) requirement to classify (class I, class II, class III) LDTs, based on risk, using a public process involving advisory panels and public comment.[109] Once classification has taken place, the FDA will enforce premarket review requirements, prioritizing the highest risk class III tests. According to the framework guidance document, "[d]evices would remain on the market during review and FDA's consideration of applications."[110]

For three subsets of LDTs, however, FDA will exercise enforcement discretion for premarket review (and quality system requirements), but will enforce other regulatory requirements, including general controls, registration and listing (or notification), and adverse event reporting. The three LDT subsets are (1) low-risk LDTs (class I); (2) LDTs used for rare diseases and traditional LDTs; and, (3) LDTs for unmet needs.[111] Registration and listing (or notification) and adverse event reporting will begin 6 months after the framework guidance is final.

For moderate-risk (class II) and high-risk (class III) LDTs, all applicable regulatory requirements will be enforced by FDA, including general controls, registration and listing (or notification), adverse event reporting, premarket review, and quality system regulation requirements. FDA intends to first focus on three types of class III LDTs with the highest risk: (1) LDTs that have the same intended use as a cleared or approved companion diagnostic; (2) LDTs with the same intended use as an already FDA-approved class III device; and (3) specific LDTs used to evaluate characteristics of blood or blood products.[112] Registration and listing (or notification) and adverse event reporting will begin six months after the guidance is final. Premarket review will begin 12 months after guidance is final for class III LDTs with the highest risk; the remaining class III LDTs will phase-in over four years. For moderate risk class II LDTs, premarket review requirements will begin after completion of the class III LDTs. An FDA-accredited third party review program will use the 510(k) process for the premarket review of most class II LDTs.[113]

The agency anticipates the entire process of bringing all LDTs into compliance will take nine years to complete. Estimates of the number of laboratories developing and conducting LDTs vary, although the American Clinical Laboratory Association (ACLA) estimates the number of laboratories may be as high as 11,000.[114] The number of LDTs that will need to be brought into

[108] Ibid., p. 11 and pp. 15-16.

[109] Ibid., pp. 16-18. Notification is a less burdensome alternative and would not require payment of a registration fee.

[110] Ibid., p. 12.

[111] Ibid., p. 11. An LDT used to diagnose a rare disease is one that qualifies as a humanitarian use device (HUD), a designation that is awarded if it will be used to test fewer than 4,000 individuals per year. A traditional LDT shares the characteristics of LDTs available at the time FDA began its policy of enforcement discretion (e.g., the LDT is interpreted by qualified professionals and not by automated instrumentation or software). LDTs for unmet needs are those for which no FDA approved equivalent exists and which are both manufactured and used within the same health care facility.

[112] Ibid., p. 12.

[113] Ibid.

[114] Testimony of The American Clinical Laboratory Association (ACLA) President Alan Mertz, in U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health, *21st Century Cures: Examining the Regulation of Laboratory-Developed Tests,* hearings, 113th Cong., 2nd sess., September 9, 2014, pp. 19-20, http://docs.house.gov/ (continued...)

compliance is difficult to evaluate, given there are no regulatory requirements currently in effect for notification or registration and listing for these tests; however, a recent analysis of the voluntary Genetic Test Registry identified 8,245 clinical genetic tests, of which 15 had gone through FDA premarket review.[115] This is likely an underestimate of the number of LDTs, given that it is only genetic tests and the registry is voluntary.

Oversight of Direct-to-Consumer (DTC) Genetic Testing

Genetic testing may be offered directly to consumers, with companies entering the market and offering health-related testing (e.g., 23andMe). Proponents of DTC genetic testing maintain that such testing provides consumers with information necessary to make better health care decisions and also that it generally empowers consumers, enhancing their autonomy.[116] However, as the field has expanded and issues related to the accuracy and utility of the tests have grown, questions have arisen generally about whether and how to regulate this type of test, and specifically about the applicability of FDA and CLIA regulatory requirements to DTC genetic testing.[117]

As FDA traditionally exercised enforcement discretion over LDTs, and because the majority of DTC genetic tests are LDTs, manufacturers of DTC genetic tests that are also LDTs have generally operated under the assumption that regulatory requirements pertaining to these tests are not actively being enforced by the FDA. (FDA-regulated ASRs contained in such tests are clearly regulated; however, not all LDTs contain regulated ASRs.) To date, the agency has not provided guidance on this issue; however, the FDA has "stated publicly that DTC genetic testing should be regulated by the agency. Several companies have decided to come to the FDA with premarket submissions, and these are in the process of working with the FDA to come into compliance."[118] Notably, the FDA states in its recently released *Framework for Oversight of Laboratory Developed Tests (LDTs)* that "FDA generally does not exercise enforcement discretion for direct-to-consumer (DTC) tests regardless of whether they meet the definition of an LDT provided in this guidance. Therefore the enforcement policies in this guidance do not apply to DTC tests, *and FDA's usual enforcement policies apply to DTC tests* [emphasis added]."[119]

Despite stating that it generally does not exercise enforcement discretion over direct-to-consumer tests, nevertheless, the agency has generally not actively enforced regulatory requirements for

(...continued)

meetings/IF/IF14/20140909/102625/HHRG-113-IF14-Wstate-MertzA-20140909.pdf.

[115] The remainder either indicated they fell under enforcement discretion (1,072) or included no information about FDA status (7,158). Testimony of AdvaMedDx Executive Director Andrew Fish, in U.S. Congress, House Committee on Energy and Commerce, Subcommittee on Health, *21st Century Cures: Examining the Regulation of Laboratory-Developed Tests,* hearings, 113th Cong., 2nd sess., September 9, 2014, p. 8.

[116] See, for example, Pascal Su, "Direct-to-Consumer Genetic Testing: A Comprehensive View," *Yale Journal of Biology and Medicine,* vol. 86 (2013), pp. 359-365.

[117] Juli Murphy Bolinger, Robert C. Green, and David Kaufman, "Attitudes About Regulation Among Direct-to-Consumer Genetic Testing Customers," *Genet Test Mol Biomarkers*, vol. 17, no. 5 (May 2013), pp. 424-428.

[118] David H. Spencer and Christina Lockwood, "Direct-to-Consumer Genetic Testing: Reliable or Risky?" *Clinical Chemistry,* vol. 57, no. 12, (December 2011) pp. 1641-1644.

[119] FDA, Framework for Regulatory Oversight of LDTs, footnote 4, p. 4.

DTC genetic tests. For example, in 2010 testimony, Jeffrey Shuren, Director of FDA's Center for Devices and Radiological Health, noted that "although FDA has cleared a number of genetic tests since 2003, none of the genetic tests now offered directly to consumers have undergone premarket review by the FDA.... "[120] However, more recently, the FDA has taken steps to enforce the regulation of certain DTC genetic tests. Specifically, in November of 2013, the agency sent a warning letter to 23andMe instructing the company to discontinue marketing of its Personal Genome Service (PGS) test until it receives FDA clearance for this test.[121]

Clinical laboratories performing health-related genetic testing on human specimens are subject to CLIA requirements, whether or not the tests are provided directly to consumers; however, regulators have had some difficulty determining whether companies offering DTC genetic testing are utilizing CLIA-certified laboratories or not.

In addition, certain manufacturer claims about their products are regulated by the Federal Trade Commission (FTC), although a full discussion of this regulation is outside the scope of this report. "Section 5 of the Federal Trade Commission Act [(FTCA, 15 U.S.C. §45)] prohibits unfair or deceptive acts or practices in or affecting commerce. Section 12 of the FTCA [(15 U.S.C. §52)] 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."[122] The truthfulness of such claims in DTC genetic testing is an issue, compounded by the fact that consumers are often ordering the test in the absence of consultation with a health care provider. Additionally, companies may modify the content of their webpages in real time, creating difficulty in enforcing regulatory requirements.

[120] Shuren, *Direct-to-Consumer Genetic Testing*, testimony on July 22, 2010.

[121] See FDA Warning Letter to 23andMe, November 22, 2013, Document Number GEN1300666, http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm. On February 20, 2014, partially in response to the FDA's warning letter to 23andMe, Senator Alexander sent HHS Secretary Kathleen Sebelius a letter requesting clarification of the Administration's position on patient access to personal health information, http://www.alexander.senate.gov/public/index.cfm?p=PressReleases&ContentRecord_id=1fa364a5-3a14-4cce-b2ed-9940c033aac3.

[122] See Shuren, *Direct-to-Consumer Genetic Testing*, testimony on July 22, 2010.

Appendix. GAO Investigations into Direct-to-Consumer Genetic Testing

GAO has carried out a number of investigations and other oversight activities related to DTC genetic testing. A 2006 GAO investigation of four companies selling DTC genetic tests found that these companies "misled consumers by providing test results that were both medically unproven and so ambiguous as to be meaningless."[123] GAO conducted a second investigation, from June 2009 to June 2010, of four different genetic testing companies, this time selecting companies that were "frequently cited as being credible by the media and in scientific publications."[124] In July 2010, GAO provided testimony on this second investigation before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce. GAO stated that the DTC genetic test results were "misleading and of little or no practical use to consumers."[125] Specifically, GAO found that identical DNA samples yielded contradictory predictions depending solely on the company the DNA was sent to for analysis. The tests in the second GAO investigation cost from $299 to $999 and provided risk predictions for diseases such as diabetes, hypertension, multiple sclerosis, leukemia, breast cancer and prostate cancer.

GAO consulted with several external experts in the field of genetics about the results of this second investigation. One expert stated that "the science of risk prediction based on genetic markers is not fully worked out, and that the limitations inherent in this sort of risk prediction have not been adequately disclosed."[126] An expert further noted "the fact that different companies, using the same samples, predict different…directions of risk is telling and is important. It shows that we are nowhere near really being able to interpret [such tests]."[127] When asked if any of the test results or disease predictions were more accurate than the others, the genetics experts stated that "there are too many uncertainties and ambiguities in this type of testing to rely on any of the results."[128] For certain situations, the external experts agreed the limitations of the tests should be "clearly disclosed upfront" and suggested that GAO attempt to obtain a refund; two companies complied, but a third refused and the fourth did not respond to the refund request.[129] SACGHS also addressed the issue of the regulation of DTC testing in its 2008 report on the oversight of genetic testing.[130]

---

[123] GAO, Direct-To-Consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices, GAO-10-847T, July 22, 2010, p. 1, http://www.gao.gov/new.items/d10847t.pdf; and GAO, Nutrigenetic Testing: Tests Purchased from Four Web Sites Mislead Consumers, GAO-06-977T, July 27, 2006, http://www.gao.gov/assets/120/114612.pdf.

[124] GAO, Direct-To-Consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices, GAO-10-847T, July 22, 2010, p. 2, http://www.gao.gov/new.items/d10847t.pdf.

[125] Ibid., p. 4.

[126] Ibid., p. 8.

[127] Ibid.

[128] Ibid.

[129] Ibid., p. 10.

[130] "There is insufficient oversight of laboratories offering such tests, and their potential impact on the public health is an increasing concern. Direct-to-consumer marketing of laboratory tests and consumer-initiated testing have the potential for adverse patient outcomes, social stigmatization, privacy concerns, and cost implications for the health care system." See Department of Health and Human Services, Secretary's Advisory Committee on Genetics, Health, and Society, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human*
(continued...)

In response to recommendations by both SACGT and SACGHS, NIH has created a voluntary genetic testing registry for all genetic tests in order to provide a central location for information on "the test's purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials."[131] This voluntary registry may include information about genetic tests that are directly marketed to consumers. Such information, including whether or not the test was cleared or approved by FDA, could allow physicians and patients to make better informed decisions about using these tests.

Author Contact Information

(name redacted)
Specialist in Health Policy
[redacted]@crs.loc.gov, 7-....

(name redacted)
Specialist in Biomedical Policy
[redacted]@crs.loc.gov, 7-....

(...continued)

Services, Washington, DC, April 2008, p. 9, http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf.

[131] For further information, see the Genetic Testing Registry website, http://www.ncbi.nlm.nih.gov/gtr/.