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FDA Regulation of Laboratory-Developed Tests (LDTs)

Laboratory-developed tests (LDTs) are a class of in vitro diagnostic (IVD) device that is designed, manufactured, and used within a single laboratory. LDTs are often used to test for conditions or diseases that are either rapidly changing (e.g., new strains of known infectious diseases) or that are the subject of advancing scientific research (e.g., genomic testing for cancer). The majority of genetic tests—a type of IVD that analyzes various aspects of an individual’s genetic material (e.g., DNA, RNA)—are LDTs.

Federal agencies involved in the regulation of LDTs include the Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS). FDA regulates the safety and effectiveness of the diagnostic test, as well as the quality of the design and manufacture of the diagnostic test, pursuant to authorities in the Federal Food, Drug, and Cosmetic Act (FFDCA). CMS regulates the quality of clinical laboratories and the clinical testing process pursuant to the Clinical Laboratory Improvement Amendments of 1988 (CLIA). This In Focus addresses only FDA’s role in the regulation of LDTs.

The regulation of LDTs has been the subject of ongoing debate over recent decades, driven in large part by the increase in the number and complexity of genetic tests over this time. In general, 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. However, the FDA traditionally exercised enforcement discretion over LDTs—choosing not to enforce applicable statutory and regulatory requirements with respect to such tests—meaning that most of these tests have neither undergone premarket review nor received FDA clearance, authorization or approval for marketing. (For more information about FDA regulation of medical devices, including premarket review, see CRS In Focus IF11083, *Medical Product Regulation: Drugs, Biologics, and Devices*.) Some representatives of clinical laboratories and manufacturers of LDTs, such as the American Clinical Laboratory Association (ACLA), have asserted that LDTs are clinical services and not medical products, and therefore should be outside of FDA’s regulatory purview. Given the growing use and complexity of LDTs and genetic tests, both Congress and the FDA have once again revisited the regulation of LDTs.

FDA Activity on LDT Regulation

FDA has, to date, focused its enforcement efforts on commercial IVD kits, which are broadly marketed, and has not generally enforced premarket requirements for LDTs. In recent years, however, FDA has indicated its intent to regulate LDTs using a risk-based approach due to the increasing number, significance, and complexity of LDTs. In 2006 and 2007, FDA published and updated draft guidance on a specific subset of LDTs called In Vitro

Diagnostic Multivariate Index Assays (IVDMIAAs). IVDMIAAs 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. The FDA never finalized its guidance concerning IVDMIAAs, and instead announced its intent to regulate all LDTs in June 2010.

October 2014 Draft Guidance

In July 2014, FDA officially notified Congress of its intent to begin regulating LDTs through draft guidance. This notification was in fulfillment of a statutory requirement in the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA, P.L. 112-144), requiring FDA to notify Congress at least 60 days before issuing any draft or final guidance on regulation of LDTs. In the October 2014 draft guidance, *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*, FDA presented the details of a risk-based framework for regulating LDTs. The framework generally identified classes of LDTs that would be (1) exempt from regulation entirely; (2) required to meet only registration and listing (or notification) and adverse event reporting requirements; or (3) required to meet registration and listing (or notification), adverse event reporting, applicable premarket review, and quality system regulation requirements. The determination to continue enforcement discretion—or to enforce certain or all applicable regulatory requirements—for an LDT would be based on risk evaluation. The agency collected comments on the draft guidance document; however, in November 2016 FDA announced that it would be delaying finalization.

January 2017 Discussion Paper

FDA summarized the comments it had received on the 2014 draft guidance in its January 2017 *Discussion Paper on Laboratory Developed Tests (LDTs)* and noted that it would not be issuing “a final guidance on the oversight of [LDTs] at the request of various stakeholders to allow for further public discussion ... and to give our congressional authorizing committees the opportunity to develop a legislative solution.” The discussion paper included a proposed framework for an approach to LDT oversight that would focus on “new and significantly modified high and moderate risk LDTs.” Previously marketed LDTs would be grandfathered and would not be expected to comply with most or all FDA regulatory requirements, such as premarket review, unless necessary to protect the public health. In addition, new and significantly modified LDTs in several specified categories (e.g., LDTs for rare diseases) would generally not be expected to comply with FDA regulatory requirements.

Key Issues in FDA Regulation of LDTs

In recent years, despite the absence of specific agency guidance on the regulation of LDTs, FDA has nevertheless begun to assert authority over LDTs. This has included direct-to-consumer (DTC) genetic tests that provide information about the risk of developing a disease or condition, or about a patient's predicted response to medications (which can facilitate precision medicine).

DTC Genetic Tests

Genetic testing has become increasingly available for direct purchase by consumers, generally over the internet, often without the involvement of a health care provider and for increasingly complex and common diseases (e.g., cancer). As FDA has historically exercised enforcement discretion over LDTs—and because many DTC genetic tests are LDTs—DTC genetic test companies had generally understood that regulatory requirements pertaining to LDT DTC genetic tests were not actively being enforced by the FDA. Notably, however, the FDA stated in its 2014 draft guidance that “FDA generally does not exercise enforcement discretion for [DTC] tests regardless of whether they meet the definition of an LDT provided in this guidance.”

Over past years, FDA has begun to enforce the regulation of certain DTC genetic tests. In November 2013, FDA sent a warning letter to 23andMe instructing the company to discontinue marketing of its Personal Genome Service (PGS) test until it received FDA clearance for this test. Again in late 2015, FDA sent letters to companies marketing DTC genetic tests without FDA clearance (e.g., Pathway Genomics, Inc.). These actions indicated that FDA is taking steps to enforce regulatory requirements—and specifically, premarket review—for DTC genetic tests that the agency considers to be higher risk.

Alongside these actions, FDA has authorized for marketing some specific DTC genetic tests, reflecting evolution in both DTC genetic tests and FDA oversight of these tests. In 2015, FDA cleared a 23andMe PGS Carrier Screening Test for Bloom Syndrome, and in late 2017, FDA provided in the *Federal Register* its “final determination for autosomal recessive carrier screening gene mutation detection system devices by exempting this type of device from premarket notification requirements, subject to certain limitations.” In April 2017, FDA cleared the first DTC genetic test that provides information about the *risk* of developing disease. This test, 23andMe's PGS Genetic Health Risk, provides consumers information about their likelihood of manifesting 10 diseases or conditions (e.g., Celiac Disease). Since then, FDA has cleared additional tests developed by 23andMe that assess the risk of developing a disease or condition.

Pharmacogenetic Testing

In the context of asserting its authority over certain LDTs, FDA has taken recent action to address DTC—as well as health care provider ordered—pharmacogenetic tests (tests examining genetic variants with a link to metabolism of medication). Many pharmacogenetic tests are offered as LDTs. FDA cleared 23andMe's PGS Pharmacogenetic Reports test in October 2018, stating that the test does not provide information about a patient's response to any

specific medication, but that it may guide discussions with health care providers by informing how a patient may metabolize some medications. FDA released a safety communication in November 2018 warning against the use of certain DTC and provider-ordered tests that claim to predict response to *specific* medications, stating that these tests' claims have not been reviewed by FDA and are not necessarily supported by evidence. There was concern that patients and their health care providers may rely on information from these tests, and make adjustments to medication and/or dosing that could be detrimental to patient health. In April 2019, FDA sent a warning letter to Inova Genomics Laboratory for marketing tests without FDA clearance or approval that claim to predict a patient's response to specific medications based on genetic variants.

Tests that inform the use of a specific medication—termed “companion diagnostics”—are addressed through FDA guidance and are a component of personalized medicine. A 2014 guidance document, *In Vitro Companion Diagnostic Devices: Guidance for Industry*, defines companion diagnostic as “an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a therapeutic product (e.g., drug) is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product.” The guidance notes that if scientific evidence is sufficient to support the use of a diagnostic with a group of therapeutics, then the diagnostic's intended use/indications for use in its labelling should refer to the specific group of therapeutic products, rather than to a specific product to increase clinical flexibility. In April 2020 FDA issued final guidance—*Developing and Labeling in vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products: Guidance for Industry*—elaborating on this point. This guidance notes that developers may consider several factors (e.g., if a specific group of oncology therapeutic products can be defined) “when determining whether their test could be developed, or the labeling for approved companion diagnostics could be revised through a supplement, to support a broader labeling claim,” thus increasing clinical flexibility for both the provider and patient.

Recent Relevant Legislative Activity

Since passage of the 21st Century Cures Act, various legislative approaches to FDA regulation of IVDs and LDTs have been considered. A discussion draft circulated in early 2017, the Diagnostic Accuracy and Innovation Act (DAIA), outlined a regulatory approach for IVDs that was risk-based and flexible. FDA responded to DAIA in August 2018 with a proposal for a novel regulatory approach, including a mechanism for precertifying certain related tests to streamline premarket requirements. In December 2018, a new draft bill based on DAIA and incorporating FDA's feedback was released, the Verifying Accurate, Leading-edge, IVCT Development (VALID) Act. The VALID Act was first introduced in the 116th Congress (S. 3404/H.R. 6102) and again in the 117th (S. 2209/H.R. 4128). In 2022, it was incorporated into the Senate user fee bill (S. 4348, Subtitle C—In Vitro Clinical Tests).

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