FDA Presents Plans to Ensure the Reliability of Laboratory-Developed Diagnostic Tests

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On July 31, 2014, the U.S. Food and Drug Administration (FDA) took important steps to ensure that certain tests used by health care professionals to help diagnose and treat patients provide accurate, consistent and reliable results. Currently, FDA regulates genetic tests as *in vitro* diagnostic devices (IVDs, also called "test kits"), if the components of the test are bundled together, labeled for a particular use, and sold to a laboratory as a unit. Such kits must undergo successful premarket review to establish their safety and effectiveness before they may be commercially distributed. Most genetic tests, however, are laboratory-developed tests (LDTs), meaning they are assembled by laboratories themselves. In the past FDA has regulated a small subset of LDTs that the agency terms in vitro diagnostic multivariate index assays (IVDMIAs). These tests use laboratory data and an algorithm (analytical tool) to generate a result for the purpose of diagnosing, treating, or preventing disease. FDA has always asserted its authority to regulate all other LDTs, but has so far declined to do so.

This approach is about to change. In its July 31 announcement, the FDA detailed the agency's plan to issue draft guidance on the development, review and approval or clearance of LTDs, which are tests used to identify patients who will benefit from or be harmed by treatment with a certain drug and aid physicians in selecting appropriate therapies for individual patients. LDTs can be used to measure or detect a wide variety of analytes (substances such as proteins, chemical compounds like glucose or cholesterol, or DNA), in a sample taken from a human body. Some LDTs are relatively simple tests that measure single analytes, such as a test that measures the level of sodium. Other LDTs are complex and measure or detect numerous analytes and are used by health care professionals to guide medical treatment for their patients. For example, DNA variations can be detected from a blood sample, which can be used to detect certain types of gene-based cancers.

Consistent with the requirements of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)[1], signed into law by President Obama on July 9, 2012, FDA notified Congress of its intention to publish a proposed risk-based oversight framework for LDTs, which are designed, manufactured and used within a single laboratory.[2] FDA's plans are described in a document entitled "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)." This guidance finalizes and takes into consideration public comment on a draft guidance issued in 2011.

FDA Commissioner Margaret A. Hamburg, M.D. explained the rationale for the agency's action, stating: "Ensuring that doctors and patients have access to safe, accurate and reliable diagnostic tests to help guide treatment decisions is a priority for the FDA. Inaccurate test results could cause patients to seek unnecessary treatment or delay and sometimes forgo treatment altogether. Today's action demonstrates the agency's commitment to personalized medicine, which depends on accurate and reliable tests to get the right treatment to the right patient."[3]

1 Section 1143 of FDASIA requires FDA to make this notification at least 60 days prior to the issuance of draft or final guidances on the regulation of LDTs, and to include in such notification the anticipated details of such action. For this reason, FDA will not publish the draft guidance or establish a docket until at least 60 days after the notification given on July 31, 2014.

2 FDA does not consider devices to be LDTs if they are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them.

3 FDA News Release of July 31, 2014.

The forthcoming guidance is intended to help companies identify the need for LTDs during the earliest stages of drug development and to plan for the development of a drug and a companion diagnostic test at the same time. The ultimate goal of the final guidance will be to stimulate early collaborations that will result in faster access to promising new treatments for patients living with serious and life-threatening diseases.

While the FDA has historically exercised enforcement discretion over LDTs, the agency noted that today these tests may compete with FDA-approved tests without clinical studies to support their use. Indeed, FDA explained that faulty lab-developed tests have led to erroneous treatment for heart disease, unneeded antibiotic use, and to cancer patients receiving the wrong therapy. To address these concerns, the LDT notification to Congress provides details of a draft guidance through which the agency would establish an LDT oversight framework, including pre-market review for higher-risk LDTs, such as those that have the same intended use as FDA-approved or cleared companion diagnostics currently on the market. The draft guidance would also propose to phase in enforcement of pre-market review for other high risk and moderate risk LDTs over time.

FDA noted it will continue to exercise enforcement discretion for low-risk LDTs, LDTs for rare diseases and, under certain circumstances, LDTs for which there is no FDA-approved or cleared test. The agency's oversight will now be based on a test's level of risk to patients, not on whether it is made by a conventional manufacturer or in a single laboratory, while still providing flexibility to encourage innovation that addresses unmet medical needs. The FDA's draft guidance will also outline how laboratories can notify the FDA that they are currently manufacturing and using LDTs, how to provide information about their LDTs, and how they can comply with the medical device reporting requirements. One year after the guidance becomes final, manufacturers of diagnostic tests considered "high risk" will be expected to apply to FDA for approval of their tests.

Major manufacturers of some companion diagnostics have long encouraged FDA to develop this type of guidance to level the regulatory playing field over lab-developed tests. For example, in December, 2008, Genentech filed a Citizen Petition to request the Commissioner of Food and Drugs require all in vitro diagnostic tests intended for use in drug or biologic decision making be held to the same scientific and regulatory standards. However, the new plan is certain to be controversial with others and the details of the new plan will be carefully analyzed by industry, healthcare professionals, and patient groups.

After the draft guidance is published and the public is alerted to the start of the comment period, the agency intends to hold a public meeting to collect additional input.

A copy of FDA's notification to Congress and a detailed explanation of the agency's plans are available here.[4]

4 http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf.

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