

FDA Investigation into Direct to Consumer Genetic Testing Companies

An Analysis

On June 10, 2010, the United States Food and Drug Administration (FDA) sent letters to five direct-to-consumer (DTC) genetic testing companies, indicating that the previously unregulated industry would need FDA clearance before continuing to market its products. Specifically, the FDA requested that the DTC firms file applications for premarket approval (PMA) to prove that their tests were accurate and scientifically sound.

The five companies that received letters are:

- Knome, Inc., regarding the KnomeCOMPLETE™ test
- 23andMe, Inc., regarding the 23andMe Personal Genome Service™
- deCode Genetics, regarding the deCODEme Complete Scan
- Illumina, Inc., regarding the Illumina® Infinium HumanHap550 array used by deCODE Genetics and 23andMe, and
- Navigenics, regarding the Navigenics Health Compass service

The FDA also sent a similar letter to Pathway Genomics Corporation regarding the Pathway Genomics Genetic Health Report, which was to be sold in Walgreens stores, requiring that the company obtain FDA clearance or approval before placing the test on store shelves.

Copies of the letters have been posted to the FDA's website, and can be accessed at <http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm111104.htm>.

Up until now, the FDA had exercised its discretion in declining to oversee the genetic testing industry. Nevertheless, it retains the authority to do so under the 1976 Medical Device Amendments (MDA), which enables the FDA to conduct premarket review of all medical devices. Premarket review is primarily meant to ensure that medical devices, which include diagnostic devices like genetic tests, are safe, effective and provide accurate results to patients and consumers.

Before receiving the FDA letters, DTC companies disputed whether the FDA had authority to regulate at-home genetic tests. First, they argued, these tests were not within the statutory definition of "medical device."

21 U.S.C. 321(h) defines "medical device" as any "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article" which 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 which is "intended to affect the structure or any function of the body." Under this definition, the FDA determined the genetic tests offered by the DTC companies listed above to be "medical devices," because they were intended for diagnosing diseases and other conditions.

Specifically, the FDA letters stated that by providing descriptions of the genetic basis for disease traits, information about how patients might metabolically respond to certain medications, including warfarin and clopidogrel, based on their genetic make-up, information on individuals' genetic bases for medication sensitivities, calculations assessing the contribution of single-nucleotide polymorphisms (SNPs) to disease risk, and calculations evaluating a patient's genetic contribution to an individual's cancer risk, DTC companies might induce consumers to make medical decisions on the basis of the information provided. Especially in the cases of drug metabolism and cancer risk, these medical decisions could be highly risky if the information provided by the tests is inaccurate or faulty. The FDA therefore concluded that oversight was necessary.

DTC companies also argued that even if genetic tests do constitute medical devices, they fall within exceptions that excuse them from premarket regulation. Under the FDA's interpretation of the MDA, not all medical devices require premarket approval. 21 U.S.C. §360c requires that the FDA assign devices to one of three regulatory classes based on the level of control necessary to assure safety and efficacy. Each class is regulated to different degree, depending on the risk it poses to consumer health.

Class I devices are those for which the general rules on adulterated substances, misbranding, etc. are sufficient to provide "reasonable assurance of the safety and effectiveness of the device." This is because (1) sufficient information exists about the efficacy of the device and (2) it does not purport to "be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health." Class I devices require no premarket submission to the FDA.

Class II diagnostic devices are those for which general controls are insufficient to ensure safety and accuracy, but "for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and other appropriate actions as the Secretary deems necessary to provide such assurance." While the FDA does not require companies to submit any filing before marketing Class I devices, companies must submit a 510(k) notice of intent to commercially market before Class II devices can be sold. A 510(k) is a premarket submission made to FDA to demonstrate that the diagnostic device is at least as safe and effective as a similar, legally marketed device that is not subject to the premarket approval application requirement.

Class III devices are the most stringently regulated. These require a premarket approval because (1) insufficient information exists to determine exactly what general or special controls are necessary to provide reasonable assurance of safety and effectiveness and (2) they are either "purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health," or they present "a potential unreasonable risk of illness or injury." Class III devices require the submission of a premarket approval, or PMA, application. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s).

In requesting PMA filings from the DTC companies, the FDA implied that they had been assigned Class III status. Alberto Gutierrez, the FDA official who signed the letters, stated in interviews that he was particularly concerned individuals might alter the dosage of important medications in response to information about their metabolism of certain drugs, or even take drastic prophylactic measures on the basis of information about genetic predisposition to serious

diseases: ““It is not unknown for women to take out their ovaries if they are at high risk of ovarian cancer,” Gutierrez told *The New York Times*. This is the kind of high-risk information that classifies these genetic tests as Class III diagnostic devices.

Gutierrez also suggested that not all genetic tests will be so strictly regulated. In other interviews, Gutierrez has said that less risky genetic tests will likely not require PMA’s, or perhaps even 510(k) filings. Gutierrez told *USA Today* that a genetic test for baldness, for example, would be categorized by the FDA as a Class I device, along with tongue depressors and elastic bandages, which require no premarket filings at all.

So why has the FDA taken so long to demand that DTC companies disclose the scientific proof behind the broad claims of their test results? Up until recently, genetic tests such as the ones DTC companies offer fit into a small exception in the pre-market filing requirements for medical devices. Since it began enforcing the 1976 Medical Device Amendments, the FDA has typically exempted Laboratory-developed Tests, or LDTs, from requiring PMA or 510(k) filings. LDTs are developed, evaluated and validated within one particular laboratory, rather than manufactured and marketed to several different labs. In explaining this rule, the FDA stated that it “viewed LDTs as relatively simple, well-understood tests that diagnosed rare diseases and conditions, and that were intended to be used by physicians and pathologists in a single institution where they were actively involved in patient care. The tests were ordinarily well-characterized, low risk diagnostic tools.” Biopsies, for example, are typically considered LDTs and not regulated by the FDA.

Up until now, almost all genetic tests have been considered LDTs, and have therefore been excluded from premarket oversight. In a departure from this policy, however, the FDA states in its letters to some of the DTC firms that “FDA does not consider your device to be a laboratory developed test because the [test] is not developed by and used in a single laboratory.” While the FDA does not include this in its letters to Navigenics or Illumina, other developments suggest it may change policy to exclude genetic tests from the LDT exemption.

In a recent announcement, the FDA stated that it would hold a public meeting this summer to discuss changes in regulation over LDTs:

“These tests, which are becoming more complex and high risk, are playing an increasingly important role in clinical decision-making. As a result, LDTs that have not been properly validated put patients at risk, such as for missed diagnosis, wrong diagnosis, and failure to receive appropriate treatment. Therefore, FDA believes that a risk-based application of oversight for LDTs is appropriate, and seeks public input on issues and concerns related to LDT oversight.” (The announcement can be accessed at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm215766.htm>)

The FDA has specifically allotted time to discuss genetic tests and the DTC industry during the meeting, suggesting that the growth of genetic testing is a prime concern in reevaluating the LDT policy.

The FDA further states in its letters that DTC firms are not excused from premarket review on the basis of the investigational device exemption (IDE). To be considered for this exemption, firms must first submit to the FDA a request to experimentally test the device, usually in preparation for a PMA or 510(k) filing. IDEs are most often filed for clinical studies or for clinical evaluation of certain modifications for new intended uses of legally marketed devices.

All clinical evaluations of investigational devices must have an approved IDE before the study is initiated. In order to qualify for this exemption, the device must have:

- An IDE approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA
- Informed consent from all patients
- Labeling for investigational use only
- Monitoring of the study and
- Required records and reports

Because DTC firms have not filed IDE's and do not comply with the requirements set out above, they are therefore not exempt from either a PMA or 510(k) filing.

Exactly how and to what extent the FDA will ultimately regulate DTC genetic testing, and genetic testing generally, is still unclear. While some details will be worked out after the July 2010 public meeting, many questions will remain. Nevertheless, the agency's request for premarket approval signals an important and necessary step towards federal oversight of emerging genetic technologies.