

Genetics and Public Policy Center

Berman Bioethics Institute
1717 Massachusetts Ave., N.W., Suite 530
Washington D.C. 20036
202-663-5971 / Fax 202-663-5992
www.DNApolicy.org

December 15, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Comments to Docket No. FDA-2008-P-0638-0001/CP

Dear Sir/Madam:

The Genetics and Public Policy Center submits these comments in support of Genentech's Citizen Petition filed on December 9, 2008.

The Genetics and Public Policy Center was founded in 2002 by The Pew Charitable Trusts with a mission to help policy leaders, decision makers, and the public better understand and respond to the challenges and opportunities arising from advances in human genetics. In 2005 the Center launched Genetic Testing Quality Initiative with the goal of improving overall effectiveness, safety, and reliability of genetic testing. More recently, the Center began a project to identify and develop policy options to address regulatory impediments to the success of pharmacogenetics.

Like Genentech, we believe that FDA has jurisdiction to regulate all laboratory-developed tests (LDTs) as medical devices and should exercise this authority in a risk-based manner consistent with its regulation of *in vitro* diagnostic (IVD) test kits. The majority of genetic tests performed today use LDTs. As we have argued elsewhere,¹ FDA's current failure to regulate these genetic LDTs – in particular genetic tests that are used in drug or biologic therapeutic decision making – threatens public health, creates serious inequities in the marketplace that disincentivize innovation, and impedes the success of personalized medicine. We address each of these concerns below.

Lack of FDA Oversight of Genetic LDTs Threatens Public Health

Today, there are genetic tests for more than 1500 diseases available clinically, and hundreds more available in research settings.² These tests are used to diagnose disease, to predict

¹ See, e.g., Javitt, G. 2007. In search of a coherent framework: options for FDA oversight of genetic tests. *Food and Drug Law Journal* 62: 617-652.

² GeneTests, www.genetests.org.

risk of future disease, and – increasingly – to guide decisions about whether to undergo a medical procedure or take a particular drug or dosage of a drug.

Yet the regulatory framework for ensuring the safety and effectiveness of these tests is both incoherent and inadequate.³ To date, FDA has cleared or approved only a handful of genetic test kits. Thus, the vast majority of genetic tests are not reviewed to ensure either analytic or clinical validity. Most genetic tests are sold as LDTs, and FDA does not regulate them. This means that there is no external review of the tests' analytic validity (their ability to get the correct answer reliably over time), or their clinical validity (the relationship between a particular genetic variation and an individual's current or future health status).

Although clinical laboratories are supposed to make evidence-based decisions about when to offer LDTs, the Genetics and Public Policy Center has identified situations where claims are not supported by the available scientific evidence.^{4,5} Ensuring adequate validation is of particular concern for tests that are intended to inform drug selection or dosing (i.e., pharmacogenetic tests). Yet today many companies offer pharmacogenetic tests, and an increasing number of these tests are marketed directly to consumers,⁶ putting the public in jeopardy if treatment decisions are based on false or misleading claims.

Some have argued that the Clinical Laboratory Improvement Amendments (CLIA)⁷ is adequate to ensure the accuracy and reliability of laboratory tests. However, CLIA is intended to ensure the quality of the conditions under which tests are performed, not the safety and effectiveness of the tests themselves. Thus, while CLIA is an important complement to FDA oversight of LDTs, it cannot substitute for FDA review. While FDA periodically has sent letters to laboratories offering LDT-based tests informing them of the need for FDA review,⁸ this episodic and seemingly arbitrary enforcement activity cannot substitute for a coherent and sustained regulatory strategy.

The Current “Two-Path” System is Inequitable and Creates Disincentives to the Development of Validated Tests

FDA regulation of IVDs and not LDTs has resulted in an uneven playing field that creates a disincentive to perform research to establish clinical validity and deters innovation of new tests with demonstrated validity. A company that invests the time and effort necessary to develop a test kit for cystic fibrosis, for example, will encounter competition in the marketplace

³ Javitt, *supra* note 1.

⁴ Hudson, K., J. Murphy, D. Kaufman, G. Javitt, S. Katsanis, and J. Scott. 2006. Oversight of US genetic testing laboratories. *Nature Biotechnology* 24 (9): 1083-1090.

⁵ Katsanis, S.H., G. Javitt, and K. Hudson. 2008. A case study of personalized medicine. *Science* 320: 53-54.

⁶ *See, e.g.* DNADirect, www.dnadirect.com/patients/tests/drug_response/index.jsp; Genelex, www.healthanddna.com/drug-safety-dna-testing. *See also* Genetics and Public Policy Center, Table of Direct to Consumer Genetic Testing Companies, available at <http://www.dnapolicy.org/resources/DTCcompanieslist.pdf>.

⁷ 42 U.S.C. § 263a.

⁸ *See, e.g.* letter from Steven I. Gutman, Director, FDA Office for In Vitro Diagnostic Devices Evaluation and Safety to David P. King, President and Chief Executive Officer, Laboratory Corporation of America, August 7, 2008, available at http://www.fda.gov/cdrh/OIVD/labcorp_itr.html. *See also* Javitt, *supra* note 1, at 649-652 (Table of 2006 FDA Letters).

from laboratories offering laboratory-developed cystic fibrosis tests that have not undergone FDA review.⁹ This current “two-path” system has resulted in very few FDA-approved test kits being available. A significant reason why many laboratories do not use FDA-approved test kits is that such tests are not available for the disorders tested for by the laboratories.¹⁰ Individual LDTs may be as reliable as those reviewed by FDA, but the public has no way to ensure that such will be the case. Thus, in addition to the potential for endangering patients, who are likely unaware that they may be receiving an unapproved test and usually lack any choice about which test they receive, this situation creates significant economic disincentives to develop validated tests.

The Success of Personalized Medicine Depends on a Coherent System of Regulation for LDTs

Many assertions have been made about the promise of personalized medicine, but few concrete examples have emerged. The goal of personalized medicine – safer, more effective drugs based on the use of genetic information in drug development, prescribing, and labeling – is predicated on the assumption that there will be valid and reliable tests available to inform therapeutic decision making. FDA has issued several guidance documents aimed at both encouraging pharmaceutical manufacturers to collect and utilize pharmacogenetic data and informing IVD manufacturers of FDA requirements when developing tests to guide therapeutic decision making.¹¹ Yet FDA’s lack of regulation of LDTs presents a gaping hole in the regulatory system needed to foster personalized medicine. If FDA regulates only drugs used as part of personalized medicine, but not the tests used to prescribe such drugs, it is missing half the equation. Pharmacogenetic drugs are only as good as the tests used in conjunction with them, and lack of FDA regulation of such tests risks undermining the safety of, and public confidence in, personalized medicine. FDA must ensure both that tests are safe and effective, and that their labeling adequately communicates to health care providers when such tests should be used and how to interpret the information they provide.

Conclusion

In summary, the Center applauds Genentech for calling FDA’s attention to a significant gap in oversight. We concur that FDA has particular expertise and insight with respect to genetic tests, and thus has a critical role to play in ensuring the safety, effectiveness, and availability of LDTs. Effective stewardship by FDA is needed to develop and implement a coherent and equitable system of oversight for such tests that is based on the level of risk posed by the test, and does not depend on whether the test is developed as an LDT or an IVD. A coherent system of oversight should (1) ensure that all genetic tests provide accurate information for diagnosis, treatment, or prevention of disease; (2) ensure that both providers and patients have sufficient information about a test’s benefits and limitations to make informed decisions about whether and

⁹ Kaufman, D.J., S.H. Katsanis, G.H. Javitt, J.A. Murphy, J.A. Scott, and K.L. Hudson. 2008. Carrier screening for cystic fibrosis in US genetic testing laboratories: a survey of laboratory directors. *Clinical Genetics* 74: 367-373.

¹⁰ Hudson *et al.*, *supra* note 4.

¹¹ Food and Drug Administration, Guidance for Industry: E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories (2008); Food and Drug Administration, Guidance for Industry and Staff: Pharmacogenetic Tests and Tests for Heritable Markers (2007); Food and Drug Administration: Pharmacogenomic Data Submissions (2005).

when to test; (3) provide a level playing field for all companies seeking to market genetic tests by establishing rational requirements that apply to all players; (4) employ a risk-based approach that tailors requirements to the degree of risk posed by a test; and (5) promote the development of new genetic tests, particularly those for rare diseases and those that can improve current treatment decision making for life-threatening diseases.

The Center looks forward to working with FDA to achieve these objectives and thereby to protect the public health, incentivize the development of new, valid tests, and achieve the promise of personalized medicine.

Sincerely,

A handwritten signature in cursive script that reads "Kathy Hudson".

Kathy Hudson
Director

A handwritten signature in cursive script that reads "Gail Javitt".

Gail Javitt
Law and Policy Director