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May 10, 2006

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

Re: Docket No. 2006D-0012

Dear Sir/Madam:

The Genetics and Public Policy Center welcomes the opportunity to provide comments on the Food and Drug Administration's (FDA's) Draft Guidance for Industry and FDA Staff: Pharmacogenetic Tests and Genetic Tests for Heritable Markers. The Center, which is supported at the Berman Bioethics Institute of Johns Hopkins University by the Pew Charitable Trusts,¹ works to create the environment and tools needed by key decision makers in both the private and public sectors to carefully consider and respond to the challenges and opportunities that arise from scientific advances in human genetics, particularly as they relate to healthcare.

The Center believes this Draft Guidance, as well as the several related documents that preceded it, represent an important step in FDA's evolving approach to oversight of genetic testing. The Center commends FDA for its recognition of the growing importance of genetic testing in health care delivery and of the need to ensure that the genetic tests used by health care providers and patients are of high quality.

Scope

The Center is pleased to note that the scope of this document includes both pharmacogenetic tests and tests for heritable markers. As the Draft Guidance correctly notes, "testing for pharmacogenetic polymorphisms and genetic mutations is the same, and yields the same general types of results," although test-specific characteristics may lead to different specific requirements.²

¹ These comments represent the views of the Genetics and Public Policy Center, and not necessarily those of The Pew Charitable Trusts.

² Draft Guidance at 2.

However, while the scope is appropriately broad regarding the type of genetic tests covered, it is unclear, and therefore potentially unduly narrow, regarding the context in which genetic tests will be subject to FDA's 510(k) or PMA requirements. While never explicitly stated, it appears that the Draft Guidance is applicable only to diagnostic "test kits," i.e., freestanding diagnostic products that laboratories may purchase to perform genetic tests, and is not applicable to tests developed in-house by clinical laboratories. Assuming this is the case, FDA's well-intentioned effort to ensure the quality of genetic testing likely will fall short of its goal.

Current Regulatory Environment

Today, there are tests for well over 900 genetic diseases available for clinical use.³ Of these, FDA has approved only about a dozen, and only four that detect variations in genes associated with drug metabolism or drug efficacy.⁴ For the vast majority of genetic tests, therefore, there is currently no mechanism to ensure their analytic and clinical validity when used in clinical practice.

To be sure, all genetic testing laboratories are subject to the Clinical Laboratory Improvement Amendments of 1988 (CLIA). These amendments were intended to strengthen the government's oversight of clinical laboratories by requiring that all clinical laboratories adhere to general requirements for quality control standards, personnel qualification, and the documentation and validation of test procedures. A key component of CLIA is the requirement of proficiency testing, meaning a method of externally validating the level of a laboratory's performance. Proficiency testing is therefore central to demonstrating the adequacy of a test's analytic performance, i.e., its analytic validity. The CLIA program mandates test-specific proficiency testing requirements through the creation of a "specialty area." Specialty areas must be developed for all "high-complexity" tests, meaning those that require higher skills to perform and interpret. But, unlike similarly highly complex tests, such as those for infectious diseases, there is today no "specialty area" for genetic tests. As one consequence, CLIA does not specify any proficiency testing requirements for genetic tests.

Moreover, even were a specialty to be instituted for genetic testing, it would not include provisions aimed at assessing the clinical validity of tests, i.e., whether the genetic mutation or polymorphism detected is relevant to a patient's diagnosis, treatment, disease risk, or risk of passing a disease on to a child. While CLIA contains a general requirement that the laboratory director ensure that the laboratory provide quality laboratory services, it does not mandate any specific type or level of data that are required to demonstrate the clinical validity of a test. Each laboratory director makes an independent judgment regarding whether the data are sufficient to warrant offering the test. Nor is there any requirement or incentive for laboratory directors to make public the

³ GeneTests, www.genetests.com.

⁴ These are tests for variations in the CYP450 and UGT1A1 genes and tests for Her-2 positive and EGFR positive tumors.

data underlying their decision, which hampers the ability of health care providers or patients to make an informed judgment about testing.

Thus, there are today no agreed upon standards for, or external review of, the vast majority of genetic tests being used in patient care to ensure that they provide information relevant to the current or future health of patients.

The Center recognizes that there are practical and resource limitations to FDA's ability currently to oversee all genetic tests. Moreover, we recognize that, when it comes to devising an appropriate regulatory paradigm to ensure the safety and accuracy of tests, one size will not -- indeed should not -- fit all. We share the concern expressed by patient advocates, laboratories, and others that regulations should not be so burdensome that they impede patient access to potentially valuable new tests. At the same time, we are troubled by the significant gaps and inequities in the current regulatory environment that may potentially undermine the promise of genetic testing and jeopardize patient health and health care provider and patient trust in the enterprise.

Regulatory Parity

The requirements for test kits that go through FDA and those that do not are significantly different. As the most recent Draft Guidance reflects, test kit manufacturers must submit data to FDA demonstrating the analytic and the clinical validity of the test kit they seek to market.

The need for regulatory parity regardless of the route to market (test kit v. laboratory-developed test) has been noted by others in comments on related FDA documents.⁵ We believe that the current regulatory regime, coupled with the agency's lack of clarity regarding the scope of its authority, is problematic because it creates a "two-tiered" system for genetic tests and encourages a route to market that entails less, rather than more, external oversight, particularly with respect to clinical validity of tests.

We would therefore urge FDA to address the intended scope of its Draft Guidance and other related documents⁶ and, at a minimum, state whether and under what

⁵ Comments of AdvaMed re: Docket No. 2004N-0279: Drug Diagnostic Co-development Concept Paper at 3 ("We also encourage FDA to work through the appropriate channels within FDA to ensure that laboratory-developed tests which generate results intended to be used by the medical community in the same/similar manner as their commercially-distributed counterparts, and pose similar public health risk(s), are regulated to the same standards defined in the guidance that stems from this Concept Paper."); Comments of Genzyme re: Docket No. 2004N-0279: Drug Diagnostic Co-development Concept Paper at 2 ("it is imperative that both [IVD and homebrew assays] be addressed in guidance.")

⁶ Drug-Diagnostic Co-Development Concept Paper (Draft), April 2005); Class II Special Controls Guidance Document: CFTR Gene Mutation Detection Systems, October 2005; Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System, March 2005; Class II Special Controls Guidance Document: Factor V Leiden DNA Mutation Detection Systems, March 2004.

circumstances the agency intends to apply them to genetic tests developed in-house by clinical laboratories.

Labeling

The current Draft Guidance addresses the labeling requirements for genetic test kits. These requirements include directions for use, a description of quality control measures to be followed, and information on interpreting and reporting results.

Accurate and sufficiently informative labeling, both on the genetic test itself and in the laboratory report, is essential to ensuring appropriate test selection and interpretation, and therefore to ensuring proper care. The health care provider is responsible for correctly using and interpreting genetic tests. To do so, he or she must know when it is appropriate to test, the correct test to order, what information the test can provide, the limitations of the test, how to interpret positive and negative results in light of the patient's medical or family history, and the medical management options available. However, studies continue to show that many health care providers are ill prepared to use genetic tests in clinical practice.⁷

For most genetic tests, there are no agreed-upon standards for what information must be provided to the clinician before tests are ordered or for how to communicate results of tests to health care providers and patients. The lack of agreed-upon standards put health care providers and patients at a disadvantage and may compromise patient care.

While the Center supports the type of information required under the Draft Guidance's labeling provisions, these provisions will have a very limited impact on the overall quality of genetic tests if applied only to genetic tests performed using FDA-regulated test kits.

Conclusion

The Genetics and Public Policy Center appreciates the opportunity to provide these comments, and looks forward to further opportunities to discuss these issues with FDA.

Sincerely,



Center Director



Law and Policy Director

⁷ Baars MJH, Hennenman L, ten Kate LP. Deficiency of knowledge of genetics and genetic tests among general practitioners, gynecologists, and pediatricians: a global problem. *Genet Med* 2005;7:605-610.