Brad Hammoor
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The Future of FDA Regulation of Pharmacogenetics

In 2007, biotechnology startup 23andMe offered consumers a biological link to their family tree. For $99 and a cheek swabbing, the service identifies and analyzes single nucleotide polymorphisms [SNP] within their genome in order to provide health-related information concerning 254 diseases and conditions as well as information on genealogy and non-disease traits.[1] Unfortunately, consumers were buying unvalidated knowledge. SNPs rarely affect health directly. Instead, SNP-based health information is typically based on statistical correlations between SNPs and phenotypic traits that are found in whole-genome association studies.[2] A physician or trained medical professional is required to put the data into perspective. In the absence of this, the data can be misconstrued. This raises the question: "Where was the FDA in 2007?" Moreover, is it the role of the FDA to oversee direct to consumer medical studies? On November 22, 2013 the FDA made the decision to halt health-related consumer genetic testing in the United States by sending a warning letter to 23andMe.[3] Although 23andMe's efforts were suspended, they were onto something. Understanding our genetics opens the door to receiving effective personalized, genetics based medical therapy. It is probable that a blue-eyed, Swede with a genetic marker for arthritis needs a different pharmacogenetic

[1] "23andME Homepage." *23andMe*. 1 Dec. 2014. Web. 7 Dec. 2014. <https://23andMe.com>.

[2] Zettler, Patricia, Jacob Sherkow, and Henry Greely. "23andMe, the Food and Drug Administration, and the Future of Genetic Testing." *JAMA Network*. JAMA Internal Medicine, 17 Feb. 2014. Web. 7 Dec. 2014.

[3] "23andMe Warning Letter from FDA." *23andMe, Inc. 11/22/13*. 22 Nov. 2013. Web. 7 Dec. 2014. <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm>.

formulation than a brown-eyed, Estonian with a genetic marker for cystic fibrosis.[4] As researchers strive to understand and treat known diseases, geneticists are working to understand why we get them in the first place. Pairing the two under a constructive FDA framework that is nimble and proactive might be the key to eradicating them. Understanding our biological family tree may very well dictate our future.

The FDA regulates genetic testing products under the classification of "devices". Although they have long considered such tests within their jurisdiction, they have not regulated many of them.[5] The FDA's primary concern with medical devices is whether they are safe and effective for their intended use. For genetic tests, effectiveness is judged by 2 concepts. First, is its analytical validity, how well it measures what it is intended to measure. Second, is its clinical validity, the accuracy of the results with regard to the presence or absence of a disease or condition.[6] For 23andMe, analytical validity meant correctly identifying single nucleotide polymorphisms and clinical validity meant accurately reporting any potential health consequences. 23andMe provided the information they promised but it was of little value to consumers without medical interpretation.[7] The FDA ordered 23andMe to stop marketing its personal genome service because it is an unapproved and uncleared device. The company's website had called its

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[4] Adam, Amy. "Personalized Medicine." *Personalized Medicine*. Genetic Health. Web. 7 Dec. 2014. <http://www.genetichealth.com/Resources_Personalized_Medicine.shtml>.

[5] "Regulation of Genetic Tests." *Regulation of Genetic Tests*. US Government. Web. 8 Dec. 2014. <http://www.genome.gov/10002335>.

[6] "23andMe Warning Letter from FDA." *23andMe, Inc. 11/22/13*. 22 Nov. 2013. Web. 7 Dec. 2014. <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm>.

[7] Janssens, Cecile. "How FDA and 23andMe Dance Around Evidence That Is Not There." *The Huffington Post*. TheHuffingtonPost.com, 27 Jan. 2014. Web. 8 Dec. 2014. <http://www.huffingtonpost.com/cecile-janssens/post_6753_b_4671077.html>.

personal genome service “the first step in prevention” which implies intent for use as a diagnostic tool or to prevent disease.[8] This, perhaps, was the tipping point for the FDA. The inherent risks of accepting partial results outweighed any conceivable consumer benefit. After 6 years of allowing an unregulated diagnostic tool to find its way into the homes of millions of consumers, the FDA finally ended their willingness to allow unverified health claims for direct-to-consumer genetic tests.

There is a role for personalized medicine but its success depends on safe and effective diagnostics. In-vitro diagnostic tests fall under the FDAs medical device authority and are classified and regulated in a risk-based manner.[9] When developing and validating diagnostic methods for wide scale consumer use, there are distinct study design considerations for their evaluation, which the FDA must address. Clarifying regulatory framework for these diagnostics and their related therapies, and resolving evolving oversight challenges will enable the development of successful pharmacogenomic tools for use in providing optimized treatments.

Pharmacogenetics is concerned with understanding and managing the relationship between genetic variation and an individual’s response to medicinal products.[10] In the long-term this so-called “personalized medicine” promises pharmacological therapies tailored to a person’s genetic makeup. However, realizing these benefits will depend on

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[8] "23andMe Warning Letter from FDA." *23andMe, Inc. 11/22/13*. 22 Nov. 2013. Web. 7 Dec. 2014. <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm>.

[9] Tezak, Zivana. "US FDA and Personalized Medicine: In Vitro Diagnostic Regulatory Perspective." *Future Medicine*. Personalized Medicine, 1 Jan. 2010. Web. 7 Dec. 2014. <http://www.futuremedicine.com/doi/abs/10.2217/pme.10.53>.

[10] "What Is Pharmacogenomics?" *Genetics Home Reference*. National Institute of Health. Web. 8 Dec. 2014. <http://ghr.nlm.nih.gov/handbook/genomicresearch/pharmacogenomics>.

development of viable commercial strategies.[11] Despite this necessary retooling of economical thinking, Pharmacogenetics has garnered considerable interest in the pharmaceutical industry and is on the threshold of making a major impact in commercial labs.[12] Given the promised precision of pharmacogenetics to determine drug response, it will be up to the FDA to provide a viable commercial framework in which they can thrive. As we have seen with the tech industry, development builds on itself at an increasingly rapid pace. If managed correctly, targeted pharmacologic therapy has the potential to mimic the tech boom.[13]

The pharmaceutical industry is a multibillion-dollar worldwide industry that relies on the discovery of medicinal compounds in order to remain profitable. The industry trade group for pharmaceuticals reported in 2001 that companies invested an estimated 30.3 billion dollars in research and development, 23.9 billion in the United States alone.[14] Additionally, the percent of drug sales allocated to research and development has increased steadily from 15.1 percent in 1985 to 20.00 percent in 1998.[15] [16] Of the total

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[11] Binzak, Barbara. "How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process." *Robert Crown Law Library- Stanford Law School*. Food and Drug Law Journal, 1 Jan. 2003. Web. 7 Dec. 2014. <http://heinonline.org/HOL/Page?handle=hein.journals/foodlj58&div=20&g_sent=1&collection=journals>.

[12] Lindpaintner, Klaus. "The Impact of Pharmacogenetics and Pharmacogenomics | Lindpaintner | Journal of Commercial Biotechnology." *Journal of Commercial Biotech*. Journal of Commercial Biotech, 1 Jan. 2003. Web. 8 Dec. 2014. <http://commercialbiotechnology.com/index.php/jcb/article/view/56>.

[13] Morell, Katie. "The Bio Boom: A Cottage Industry Around Cheap Genomics." *Qualcomm Spark*. Qualcom Spark, 4 Jan. 2013. Web. 8 Dec. 2014. <http://spark.qualcomm.com/salon/bio-boom-cottage-industry-around-cheap-genomics>.

[14] "Pharmaceutical Industry Profile 2004." PhRMA, 1 Jan. 2004. Web. 8 Dec. 2014. <http://www.trinity.edu/sbachrac/drugdesign/Drug Costs Articles/Phrma 2004 review.pdf>.

[15] Ibid.,

[16] Binzak, Barbara. "How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process."

money that was invested in research and development in 1999, approximately 36 percent is spent on preclinical functions, 29.1 percent on phase I, II, and III human drug trials, and 11.7 percent was spent on phase IV post-marketing human drug trials.[17] The cost of marketing a new drug is extremely high. Estimates of the total cost of bringing a new drug to market were set at 54 million dollars in 1976, 231 million dollars in 1987, and 802 million dollars in 2000.[18] Clearly the current drug market is a big business with a high level of inertia and barrier to entry.

In addition to the fiscal costs involved in bringing a new drug to market, there is a massive time cost in both developing the drug and waiting for FDA approval. The total time for drug development from development to approval rose from 8.1 years in the 60s to 14.2 years in the 80s. Between the 1980s and 1990s, the preclinical phase of drug development increased from 5.9 to 6.1 years, the clinical phase from 5.5 to 6.3 years, and the approval phase decreased from 2.8 to 1.8 years.[19] The Boston Consulting Group reported the total time to market for a new drug at 14.7 years.[20] The overall trends show that drug companies are performing more and lengthier human clinical trials while the FDA has improved its drug approval process. Because of the time and cost involved in developing a new drug, the pharmaceutical industry is seeking ways to streamline the development process. The use of genetic data in designing new medicines may be the key

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[17] Ibid.,

[18] "A Revolution in R&D: How Genomics and Genetics Are Transforming the Biopharmaceutical Industry." The Boston Consulting Group. Web. 8 Dec. 2014. <http://www.bcg.com/documents/file13745.pdf>.

[19] "Pharmaceutical Industry Profile 2004." PhRMA

[20] "A Revolution in R&D: How Genomics and Genetics Are Transforming the Biopharmaceutical Industry." The Boston Consulting Group.

to rethinking and implementing drug therapy strategies.[21] Overall, the Boston Consulting Group has estimated that genomic technologies could save drug companies an average of 300 million dollars and two years per new drug from increased efficiency.[22] For these reasons, the FDA will be forced to face the regulation of new products resulting from genetic technologies. In order for them to foster the new technology, which will have a high mandate from pharmaceutical companies, the FDA must continue to reduce the time for approval of drugs while maintaining the level of safety and efficacy requisite for approval.

There are several opportunities for regulatory change in the preclinical stage of drug approval to reflect the increasing usage of pharmacogenic data. According to Dr. Barbara Binzak of the Mayo Clinic, there is a great deal of room for improvement in the IRB stage of development. She stated that "given the enormous impact that pharmacogenomics is going to have on the pharmaceutical industry the FDA should change its regulations to provide for the presence of a geneticist on the IRB at all times."[23] The presence of a geneticist would help to expedite internal review and allow for a more thorough understanding of what the project hopes to attain. In a similar vane, Dennis O'Kane, also of the Mayo Clinic, wrote "there is a lack of understanding of FDA requirements by those regulated by the Clinical Laboratory Improvement Amendments. Conversely, I suspect the FDA is not fully aware of some of the issues and ramifications

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[21] Morell, Katie. "The Bio Boom: A Cottage Industry Around Cheap Genomics."

[22] "A Revolution in R&D: How Genomics and Genetics Are Transforming the Biopharmaceutical Industry." The Boston Consulting Group.

[23] Binzak, Barbara. "How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process."

of regulation for practicing physicians and laboratorians."[24] He proposes that a critical overhaul in education pertaining to FDA oversight must take place in order to rectify these differences. An overhaul of preclinical practices will help in advancing the cause of personalized medicine.

Once preclinical studies have been concluded, the issues with safety in clinical trials are the next major step for the FDA. The immense number of medicines that could emerge from pharmacogenomics will likely place an immense burden in the safety considerations of the FDA.[25] With each medicine tailored to a specific patient, the FDA could be forced to examine medicines on an individual basis. Binzak suggested a workaround to the complication: "because the clinical process uses healthy volunteers in the initial stages and affected individuals in the later stages, it is important that the FDA require drug sponsors to clearly define which subgroups of individuals, based on their genetic profiles, fall into which category."[26] Her idea of using overarching genetic profiles to categorize patients could help in speeding up the review process while still maintaining the strict requirements for deployment to the greater public. Once a drug is on the market, drug sponsors often continue to monitor the reporting of adverse drug reactions.[27] Binzak further recommends that the FDA should demand a phase IV study as

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[24] O'Kane, Dennis. "An Outsider's Viewpoint: The FDA Should Regulate Clinical Pharmacogenetic/ Genomic Tests, But..." *Nature*. Nature, 1 Dec. 2010. Web. 7 Dec. 2014. <http://www.nature.com/clpt/journal/v88/n6/full/clpt2010235a.html>.

[25] "FR Doc 04-18360." *FR Doc 04-18360*. FDA, 11 Aug. 2004. Web. 8 Dec. 2014. <http://www.fda.gov/OHRMS/DOCKETS/98fr/04-18360.htm>.

[26] Binzak, Barbara. "How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process."

[27] "U.S. Food and Drug Administration." *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*. US Government. Web. 8 Dec. 2014. <http://www.fda.gov/Safety/MedWatch/>.

a requirement for drug approval since it will improve market safety. Because a phase III trial may only include several thousand people, a drug with an adverse response in 1 out of 50,000 patients, for instance, may escape detection.[28] Due to such scenarios, post-clinical testing would be a necessity. The FDA clearly acknowledges the future of pharmacogenomics regulation but there are still many steps to take in order to properly prepare.

New legislation such as the US Food and Drug Administration Act (FDAAA) of 2007 and the Genomics and Personalized Medicine Act of 2010 have tried to address the gaping holes in the new approval regime. The FDAAA marks the most profound reworking of US drug regulation since 1962.[29] It reshapes how evidence will be generated and applied in the period of a drug's life, which is an important period for Pharmacogenomic research. The FDAAA envisions successive improvement of the risk-benefit ratio for new drugs by developing new metrics such as tests that predict patients' response to the drug. While the FDAAA expanded the FDAs authority to require post-market clinical trials, it crucially diversified the agency's sources of evidence to allow a greater use of observational methodologies in the post market period. The act also calls for creation of a 100 million-person post-market risk identification and analysis system that will harness administrative data, pharmacy purchase records, and clinical data in electronic form. The system will support public health uses such as drug safety

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[28] "Pharmaceutical Industry Profile 2004." PhRMA

[29] Evans, BJ. "Establishing Clinical Utility of Pharmacogenetic Tests in the Post-FDAAA Era." *Nature-Clinical Pharmacology and Therapeutics*. Nature, 1 Dec. 2010. Web. 7 Dec. 2014. <http://www.nature.com/clpt/journal/v88/n6/full/clpt2010237a.html>.

surveillance, but congress also calls for its use in advanced analysis.[30] Given the additional complexity involved in genetic medicines, the overarching control and monitoring mechanisms put in place by the FDAAA is a positive step in enforcing the FDAs regulation of safety and efficacy of new drugs.

Similarly, the Genomic and Personalized Medicine Act was written to secure the promise of personalized medicine by expanding and accelerating genomics research. The bill established a committee to carry out a comparative analysis of laboratory review requirements under the Clinical Laboratory Improvement Amendments. Principally, the committee sought to assess and reduce unnecessary differences in these requirements and to eliminate redundancies, decreasing the burden of review for the FDA. The bill also seeks through the FDA to develop a companion diagnostic test whenever a new drug application is submitted in order to address significant safety concerns. The bill instructed for a companion test to be developed when data from post-marketing clinical trials demonstrate significant safety or effectiveness concerns with use of the marketed drug. Finally, the bill would establish an Office of Personalized Healthcare within the Office of the Secretary of Health and Human Services to coordinate the activities related to genomics and personalized medicine of the Department of Health and Human Services and other relevant federal agencies, and private as well as public entities.[31] While the act has clear implications for general regulation of drugs and tests under the jurisdiction of

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[30] "Food and Drug Administration Amendment Acts." US Government, 27 Sept. 2007. Web. 8 Dec. 2014. <http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/html/PLAW-110publ85.htm>.

[31] "Genomics and Personalized Medicine Act of 2010." *Bill Text*. Library of Congress, 27 May 2010. Web. 7 Dec. 2014. <http://thomas.loc.gov/cgi-bin/query/z?c111:H.R.5440:>.

the FDA, it is the first to explicitly address the growing issue of pharmacogenomics in the industry and how they can be properly integrated into society.

With the changing landscape of regulatory procedures, it was surprising that at the same time the FDA was ending the operations of 23andMe they were authorizing Illumina's newest sequencing products: a sequencing platform, 2 tests for cystic fibrosis, and a universal kit for laboratories to develop their own tests.[32] The FDAs authorization of the high throughput-sequencing platform was presumably based on a favorable assessment of their analytical validity. The authorization was not, however, accompanied by a requirement that the analytical validity of the testing be demonstrated. The FDA has said, without disclosing details, that it is interested in a risk-based approach to regulating genetic tests that are developed by laboratories. Stronger regulation would be applied to tests that are deemed riskier.[33] This does not, however, mesh with the overarching ideology of proposed tests needing clear validation. For example, although the clinical validity of some gene variations is well known, such as the variations that lead to cystic fibrosis, many stretches of DNA have either only weak evidence for their health effects or are simply variants of unknown significance.[34] The agency's nearly simultaneous authorization of the first next-generation genetic sequencing products marks the beginning of large-scale whole genome and exome sequencing for clinical use. But the

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[32] Zettler, Patricia, Jacob Sherkow, and Henry Greely. "23andMe, the Food and Drug Administration, and the Future of Genetic Testing."

[33] Collins, Francis, and Margaret Hamburg. "First FDA Authorization for Next-Generation Sequencer — NEJM." *New England Journal of Medicine*. New England Journal of Medicine, 19 Dec. 2013. Web. 7 Dec. 2014. <http://www.nejm.org/doi/full/10.1056/NEJMp1314561>.

[34] Annas, George. "23andMe and the FDA." *New England Journal of Medicine*. New England Journal of Medicine, 13 Mar. 2014. Web. 7 Dec. 2014. <http://www.nejm.org/doi/full/10.1056/NEJMp1316367>.

application of these technologies also depends on the standards for clinical validity. Requiring proof of clinical validity for each variant would halt most, if not all, genetic testing. But if the FDA does not require any evidence of clinical validity, it would invite significant future problems.

From 23andMe to Illumina, it is clear that the FDA must continue to rectify its regulatory procedures in order to appropriately prepare for the coming pharmacogenomics revolution. The pharmaceutical industry is one of the largest in the world, with immense research and development costs.[35] These costs are often imposed on the consumer, limiting the demand for such drugs. It has been shown that by adapting medicine fabrication techniques through genetics these costs can be significantly lowered.[36] The time to research and develop these drugs can also be lowered significantly through genetics. Scholars have recommended many simple adaptations to the current investigative structure in order to try and meet these goals.[37][38] Additionally, governmental entities, such as congress and the FDA, have proposed and enacted bills with specific intent to regulate genetically based medicines. The Food and Drug Administration Act of 2007 was the first motion from regulatory agencies since 1962 and the following Genomics and Personalized Medicine Act made a clear statement that the FDA is attempting to address the growing industry and foster it in such a way that it is safe and

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[35] "S&P Industry Rankings." *The Standard and Poor's Five Hundred*. Business Week. Web. 8 Dec. 2014. <http://www.businessweek.com/pdfs/2004/0414_bw50industries.pdf>.

[36] "A Revolution in R&D: How Genomics and Genetics Are Transforming the Biopharmaceutical Industry." The Boston Consulting Group.

[37] Binzak, Barbara. "How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process."

[38] O'Kane, Dennis. "An Outsider's Viewpoint: The FDA Should Regulate Clinical Pharmacogenetic/ Genomic Tests, But..."

effective. The lessons learned early in the personalized medicine movement will be sure reminders for the FDA moving forward, but the strength of the industry relies on safe and effective regulation. In order for pharmacogenomics to save lives on a massive scale the FDA must continue to modify its current procedures. The integration of Pharmacogenomics into society will be a world changing revolution in how we think about and deal with disease. The potential for life changing applications will force the FDA to construct framework that is nimble and proactive might be the key to eradicating them.

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