An Unfulfilled Promise:
Changes Needed to the Drug Approval Process to Make Personalized Medicine a Reality

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I. INTRODUCTION

The Food and Drug Administration (FDA) serves as the primary regulatory gatekeeper for health products entering the American market. While not always ideal, for most of the twentieth century, the statutory rubric of the Federal Food, Drug, and Cosmetic Act (FDCA), the main statutory foundation for FDA's authority, has worked quite well. In 1962, FDA gained authority to regulate not just safety, but efficacy, of drugs. In the decades following, with limited congressional assistance, FDA has stretched and twisted its authority to deal with new technology. In 1976, that authority was extended to devices. In the latter decades of the century, FDA's authority has been applied to regulate technologies such as cellular products, software, and genomic testing. FDA has approved thousands of products and for most of the twentieth century, despite periodic complaints about the length of time to approval, most stakeholders have been generally satisfied with the overall approval process, if not specific decisions within that process.

But this model is applicable to the production of products for widespread use in the general population based on twentieth-century notions of disease and therapy. With limited exceptions, an approved product is designed to be used by anyone affected by a specified condition, often many hundreds of thousands of people. In 2004, the Vioxx experience revealed some of the holes in that rubric because only after approval did it become clear that a segment of the population using the drug suffered cardiovascular effects. But that problem, which exposed potential for existing but limited human variability in drug response in a drug that was mostly safe and effective for a large population, is fairly resolvable through better postmarketing surveillance. It is less clear that the overarching structure of the FDCA can effectively deal with one of the most promising innovations of the twenty-first century—personalized medicine—which not only exposes human variability, but embraces it. Current attempts to harmonize the demands of personalized medicine with the requirements of the FDCA involve the inclusion of pharmacogenomic information in product labeling and the development and

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1 See, e.g., Simon Frantz, How to Avoid Another Vioxx, 4 NATURE REVIEWS DRUG DISCOVERY 5, 5 (2005). The problem was identified through clinical trials.

2 Food and Drug Administration Amendments Act of 2007 (FDAAA) gives FDA express authority to require a Risk Evaluation and Mitigation Strategy (REMS) for drugs upon approval and following approval if FDA determines that a REMS is needed to ensure that the benefits of a drug outweigh its risks. Federal Food, Drug, and Cosmetic Act (FDCA) § 505-1(a), 21 U.S.C. § 355-1 (2012). FDA also has the power to require safety-related labeling changes and postmarket studies. FDCA § 505(o), 21 U.S.C. § 355(o) (2012).
validation of companion diagnostic tests.\textsuperscript{3} Even these attempts have faced difficulties and have been only moderately successful. Moreover, FDA's authority to regulate in even that limited context is not clear. And these preliminary steps do not fully grapple with the ultimate goal of personalized medicine: treatment, including specific products, tailored to the individualized needs of a single patient.

Personalized medicine demands the development of products applicable to small sub-populations rather than our current model of product development for large populations. The FDCA structure does little to incentivize clinical trial design that is designed to expose variation rather than minimize it. The typical approval process takes years and involves approval of a clearly defined product with a specific indication in a specific population. The economics of the drug approval process drives drug sponsors to limit variation in the populations studied. To do otherwise would be cost prohibitive. Moreover, the pharmaceutical industry is experiencing decreased research and development productivity.\textsuperscript{4} Physicians are ill-prepared to take up the slack and personalized medicine will change their world as well. With health reform and cost pressures, our overall regulatory response to health products and technology is already subtly but rapidly changing. Our hopes for personalized medicine may be the straw that breaks the back of our current rubric—or stubborn adherence to our twentieth century notions may fatally stymie the development of personalized medicine.

To achieve the ambitions of personalized medicine, we will need a dynamic future pathway which will most likely require statutory changes. This article explores some of the potential pathways as they affect FDA's role in this process. Part II describes personalized medicine in more depth and also the context of how that term will be used in this article. Part III describes the gaps that exist in the current drug approval process as applied to personalized medicine. Part IV describes current attempts to address issues that relate to personalized medicine and how successful they are at achieving those goals. Part V briefly describes how to address some of the systemic problems. Some of these changes might be possible within the current statutory structure but real effective change would require significant amendments to the FDCA and might involve changes that would have significant changes to the health care system generally and FDA's relationships within it.

\section*{II. What Is Personalized Medicine?}

"Personalized Medicine" is "the tailoring of medical treatment to the individual characteristics of each patient . . . to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.


Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. In its broadest sense, personalized medicine includes all types of medical therapies: drugs, biologics and the many products included under the “device” rubric. This article, however, does not focus on devices other than those used in combination with drugs and biologics as diagnostic tests, because they have a different regulatory pathway and moreover, in many instances, the personalization may require adjustments more in degree than in kind. Instead, the focus of this article is on the development of personalized drugs and biologics and/or the regimens in which combinations of diagnostic devices and drug and biologic products might be used. In addition, the scope of this article includes but is broader than what is now frequently called “precision medicine,” because it does envision, at least sometimes, the development of unique treatments for an individual or small sub-group of individuals.

Typically, personalized medicine combines diagnostic methods with targeted therapeutic interventions. An example of a current use of personalized medicine is Herceptin® (trastuzumab), a monoclonal antibody that is used to treat breast cancers with specific genetic characteristics. Since Herceptin has been shown to be effective only for tumors that overexpress HER2 and the drug has serious, identified risks, it is necessary to test the tumor before treatment is considered to assure a reasonable risk-benefit ratio. Thus the treatment involves choosing an appropriate diagnostic method and then treating only those patients whose tumors meet the genetic criteria. Similarly, patients with metastatic colon cancer whose tumors have a specific form of the KRAS gene are not good candidates for treatment with Erbitux® (cetuximab).

While personalized medicine is currently most discussed in the context of cancer, the goals of personalized medicine extend to all potential disease and injury or even conditions which are not yet symptomatic. For example, recent research has revealed that Zofran® (ondansetron) may be a more effective alcohol addiction treatment for people with a certain genotype. The ultimate goal of “personalized medicine” is that we might be able to predict a given person’s susceptibility of developing disease, and, should we be unable to prevent it, the course of their disease, and to provide new targeted treatments for that specific disease and patient.

Until recently, personalized medicine has been more hype than reality. And it is still a long way from becoming the dominant part of the health care product market. While declining, the blockbuster model, involving products that are used by large swaths of the population, has been increasingly supplanted by personalized medicines that are targeted to smaller sub-groups of individuals. This shift is being driven by advances in genomics and proteomics, which have revealed new targets for drug development, and by the recognition that patients respond differently to the same drug.

5 President’s Council of Advisors on Sci. & Tech., Priorities for Personalized Medicine 1 (2008).


7 The current focus of these diagnostic methods is on genomic characteristics but proteomic methods such as those using protein biomarkers are becoming more prevalent and existing methods like imaging and other phenotyping which identify variation are equally valid.

8 See About Herceptin, Herceptin, http://www.herceptin.com/about (last visited Apr. 15, 2015). It is also being studied for other types of cancers that overexpress HER2.


11 One of the challenges will be accurately predicting who is truly likely to develop a condition—or we risk over treating people who would never become symptomatic.
population and gross more than $1 billion a year, is still the ideal—both for the purpose of making money and for generalized care given the current technological capabilities in health care. But this is changing. The Personalized Medicine Coalition describes rapid growth, reporting an increase from 13 prominent examples of personalized medicine in 2006 to 113 prominent examples in 2014.12

Many of the obstacles to achieving our goals for personalized medicine are scientific;3 we understand some of what that genetic code means, but there is a vast amount we don't know. First, there is considerable variation among human genomes.14 Second, very few diseases are caused by single genetic mutations; most disease involves multigene interactions and may also involve parts of the genome that are not even considered parts of genes. Indeed, the part of the genome that we used to call “junk DNA” may play a crucial role in human physiology. Instead of genetic medicine, we now talk about “network” medicine.15 This reflects a new understanding that disease is usually not the consequence of a single genetic mutation, but involves a much more complex process. Alterations within a cell’s DNA may be affected by other parts of the genome, other parts of the cell, other cells, or the environment (social as well as physical). We are just beginning to understand how the information in the genome is expressed and how different conditions may affect that expression.16

In short, it is all a lot more complex than people imagined when the successful mapping of the human genome was published in 2004. While the science has advanced, the translation of that science to the products and treatments that were promised ten years ago have not been realized in the public's expected time frame. In at least one way, that may actually be good. It gives us time to consider how to regulate the technologies that will develop so that the regulatory framework does not serve as an even more difficult obstacle once the science catches up to expectations. Personalized medicine challenges the regulatory rubric we have in place. The statutory structure of the FDCA is not designed to incentivize individualized treatments; it is designed to incentivize whole population treatments. While “biomedical science has developed randomized, controlled clinical-trial methods that can distinguish treatment effects from the noise of human variability,”17 as law professor Barbara Evans has noted, “the eliminated ‘noise’
is precisely what is interesting." In addition, our current rubric reflects notions of disease that lack the richness and complexity that personalized medicine demands. We cannot achieve personalized medicine without a new understanding of how to use huge data sets that are derived from multiple parts of the health care sector and networked to serve individual needs.

Personalized medicine seeks to target the treatment so that it is maximally effective and minimally toxic for the specific population for which it is created. In some instances, that population could conceivably consist of one person. For example, in cancer, creating that treatment may eventually consist of sequencing the individual's whole genome to better understand the person's overall physiology and drug metabolism and sequencing the individual's cancer mutation and testing drugs directly on the patient's excised tissue—and that of patients with similar tissue mutations—to develop an ideal targeted drug or combination of drugs. Thus the ultimate regimen that is used as part of the treatment may not actually exist until the patient is presented. This raises a number of issues. Just that one patient may require a significant amount of diagnostic testing involving tests that may not be validated or approved. Moreover, if the resulting "drug" is considered a "new drug" it cannot be used outside of a research context until it undergoes testing and approval for safety and effectiveness. Then there is still the consideration of whether the diagnostic and the "drug" should be used in combination with each other. In an individual case involving serious disease, that would be cost prohibitive and by the time it was approved, the patient would likely be dead. Thus personalized medicine will demand at least two pieces that do not presently exist: mechanisms to elucidate and treat variability in real time and a nimble regulatory process that can quickly and effectively respond to that variability.

While there was a flurry of activity and discussion about the regulation of personalized medicine right after the announcement of the success of the Human Genome Project, that activity ebbed for a number of years. Recently, there are signs of renewed focus. For example, in 2011, the National Academy of Sciences published a report calling for a new taxonomy of disease designed to support networked medicine as the foundation for future growth in precision medicine. In 2013, FDA published a report summarizing its activities designed to deal with personalized medicine. But FDA has just begun


20 The "easy" part of this is the ideal of co-developing companion drugs and diagnostics, which is itself difficult to do under the current rubric. For one thing, the approval process is currently handled by least two separate FDA centers, Center for Drug Evaluation and (CDER) and Center for Devices and Radiological Health (CDRH), which operate with different statutory requirements and standards. See infra text accompanying notes 94–95.


24 See NAT'L RESEARCH COUNCIL, supra note 6.

to wrestle with the new regulatory paradigms that all of this will require. The time to 
wrestle with these issues is now, before personalized medicine fully matures. Moreover, 
this may be a propitious time for such reform because health care reform is driving 
major changes in our health research and delivery frameworks anyway. If we wait for 
the science of personalized medicine to fully mature, those frameworks will have already 
been cemented and may actually work against personalized medicine.

III. How Gaps in Current Paradigms of Product Approval 
Affect the Development of Personalized Medicine

FDA, which has primary responsibility for medical product approval in the United 
States, derives its authority to regulate drugs and devices from the FDCA, which defines 
drugs and devices and FDA's authority to regulate them as "articles" in interstate commerce. Thus, FDA regulates products; it does not regulate the practice of medicine 
or the use of approved products. It also means that FDA necessarily approves products 
one at a time as they are presented to the agency. While FDA retains significant power 
because it has the power to demand the methods of proving that a product meets statutory 
requirements, it has limited power to demand that the clinical trials it requires include 
assets that might benefit future product development if the study designs meet the 
statutory requirements otherwise.

A. Phenotypic Disease Taxonomy Defines Product Indications

Drugs are defined under the FDCA as products that may be used to diagnose or treat 
a disease, to affect body function, or to be a component of a product that is otherwise a 
drug. That definition affords FDA considerable flexibility, which it has not hesitated 
to use over the decades since the FDCA was first legislated. Nonetheless, the key 
attribute of a drug, defining its approval and labeling, is its indication, and FDA 
continues to approve indications based on decidedly twentieth-century notions of 
disease. Most indications for use granted by FDA are specified by disease phenotype,
i.e. how and where in the body the disease symptoms manifest, rather than by the pathophysiological processes that are actually causal for the condition.\textsuperscript{31} So, for example, Tykerb® (lapatinib) is approved for metastatic breast cancer for patients whose tumors overexpress HER2 and are resistant to Herceptin® (trastuzumab).\textsuperscript{32} This is not to say that indications for use ignore recent genomic or proteomic discoveries, as this example of lapatinib is specific for HER2+ tumors. But even these indications mix tumor site with the underlying oncological mechanisms being targeted, and therefore are predicated on the traditional phenotypic disease descriptor. One effect of that is that while the mechanism of action of the drug is described in the label, it is not fully explored. The data included may or may not be applicable to other potential uses of a drug that may implicate the same mechanism of action.\textsuperscript{33} For example with lapatinib, the tyrosine kinases it targets may be important in the treatment of many other solid tumors, notably gastric cancers. Another example, sildenafil, was developed as an antihypertensive, approved originally for erectile dysfunction (Viagra\textsuperscript{®}),\textsuperscript{34} and ultimately also approved for primary pulmonary hypertension (Revatio\textsuperscript{®})\textsuperscript{35}—all based on its particular mechanism of action, which is dilation of certain vessels.\textsuperscript{36} Similarly, etanercept (Enbrel\textsuperscript{®}), currently indicated for rheumatoid arthritis,\textsuperscript{37} may be effective for asthma, based on its particular anti-inflammatory actions.\textsuperscript{38} Another important example is antibiotics where the approval is driven more by infection site (e.g. treatment of pneumonia caused by susceptible organisms) than by the organisms themselves.\textsuperscript{39}

This has important implications for the development of personalized medicine. By focusing on phenotype rather than on the pathophysiologic pathway, the mechanism of action is not fully studied; it does not account for the entire physiologic pathways

\textsuperscript{31} For example, FDA regulations describing the phases of clinical investigation assume a phenotypic indication: "Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study . . . ." 21 C.F.R. § 312.21(b) (2015) (emphasis added).


\textsuperscript{33} In addition, the data may not be produced in a standardized format that would allow further study by others; in fact, the developer may have every incentive to make such further use more difficult.

\textsuperscript{34} Vi\textit{agra}, Food & Drug Admin., http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020895s003lbl.pdf (last updated Jan. 2010).

\textsuperscript{35} \textit{Highlights of Prescribing Information (Revatio)}, Food & Drug Admin., http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021845s011,022473s004,0203109s002bl.pdf (last updated Jan. 2014).


\textsuperscript{39} See, e.g., John H. Rex et al., A Comprehensive Regulatory Framework to Address the Unmet Need for New Antibacterial Treatments, 13 Lancet Infectious Diseases 269, 271 (2013).
implicated and may not account for individual variation with that action. This may be fine if your goal is to develop treatments for larger populations, but it leaves sub-groups of people untreated and also means that even populations that may benefit may not benefit to the full extent possible or may suffer risks that could be avoided. In addition, other uses for the drug may be completely ignored. Because of the structure/function piece of the FDCA drug definition, FDA has all the authority it needs to embrace a more biologically driven method of describing intended use. But FDA does not have the authority to require the standardization, clinical trial design and data reporting that would actually make that method effective for personalized medicine.

B. Drug Approvals are Often Based on Secondary Indications and Narrow Uses

The FDCA requires drugs to be shown to be safe and effective; efficacy standards are met by demonstrating “substantial” evidence of effectiveness under the conditions of use prescribed. To meet that standard, FDA generally requires a minimum of two “adequate and well-controlled investigations.” In fact, the statute allows for considerable flexibility and FDA has tapped that flexibility to allow for fewer or varied requirements under exigent circumstances, for example, diseases like AIDS that are rapidly and dangerously spreading or for rare diseases. Effectiveness is more than efficacy. A drug developer must show not only that the drug can work but rather that it does work. To do so, FDA generally requires developers to show significant clinical benefit in a defined patient population. The term “clinical benefit” can be interpreted in a number of ways depending on the intended use. For example, in cancer, it is generally accepted to mean that the therapeutic agent demonstrates an improvement in survival compared with no therapy or to a known effective therapy, equivalence or non-inferiority to a known effective treatment, or sometimes, improved response with

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41 Id. But FDA allows one study to suffice if it meets statistical requirements, Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices, 60 Fed. Reg. 39,180, 39,181 (Aug. 1, 1995) (later codified by the Food and Drug Administration Modernization Act of 1997 (FDAMA) § 115, 21 U.S.C. § 355(d)), but it is the exception rather than the norm.
44 As was experienced with the recent controversies about Avastin, even survival is a controversial endpoint. See Proposal to Withdraw Approval for the Breast Cancer Indication for Avastin (Bevacizumab), Docket No. FDA-2010-N-0621, 7 (Nov. 18, 2011) (Commissioner’s decision) (indicating that “increased overall survival, better quality of life, or even a substantial increase in ‘progression free survival’ may serve as satisfactory endpoints). Approval of Avastin was withdrawn because follow-up studies did not corroborate the substantial increase in progression free survival that the original study demonstrated, on which FDA based its decision to grant accelerated approval. Drug companies may advocate “progression free survival” rather than overall survival as an endpoint. Arguably, the former favors quality of life but the latter is a better barometer of overall efficacy.
45 See, e.g., Letter from Richard Pazdur, Director, Division of Oncology Drug Products, Center for Drug Evaluation and Research, to Joanna Waugh, Director, Drug Regulatory Affairs, Hoffmann-La Roche Inc. (June 15, 2005), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2005/020896s016ltr.pdf (approving Xeloda® (Capecitabine) as a single-agent adjuvant treatment for Dukes' stage C colon cancer based on a demonstration of non-inferiority in disease-free survival to bolus 5-fluorouracil plus leucovorin (5-FU/LV)).
improved quality of life. Superiority is not required. Moreover, "does work" does not mean that the drug works for any individual. It merely means that it demonstrated benefit for a statistically significant portion of the tested population.

Not only does our current approval process not account well for human variability, but a drug sponsor that eliminates as much of that variability as possible during the clinical trial process will spend far less time and money in getting its product approved. Thus if a product may potentially be used for a number of conditions or diseases, the sponsor will seek the best return on investment. To do so, the sponsor will often target a disease or condition exhibiting the least variation, often a secondary indication, for initial approval. A product sponsor benefits from eliminating variability, and therefore cost, in the clinical trial phase of drug approval. Moreover, the sponsor may not suffer economic consequences by choosing a limited target after approval since with few exceptions, physicians may prescribe any approved drug “off-label” for any condition regardless of the condition for which it was approved. The sponsor may or may not seek specific FDA approval for additional conditions down the road. When it does so, its motivation is more likely to be to make the product more widely available for reimbursement. Outside of reimbursement concerns, there is little additional incentive for drug sponsors to seek new approved indications especially if a drug has lost patent protection and can no longer command high prices. This means that many “off-label” uses are essentially experimental with little data to support safety and efficacy.

C. The Current Approval Process is Purposely Not Designed to Consider Individual Efficacy but Physicians are Ill-Prepared to Bridge the Gap

The proof of safety and effectiveness required for drug approval is based on the intended patient population. The focus is on whether the drug is safe and effective for the average user in that population, not on whether it is effective for a particular individual. That choice was intentional. At the time of the passage of the 1962 Amendments which

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47 Most new drugs are not tested against existing therapies; many are approved based on superiority to placebo. Nor does FDA require comparative effectiveness data in drug labeling. Randall S. Stafford et al., New, but Not Improved? Incorporating Comparative-Effectiveness Information into FDA Labeling, 361 NEW ENG. J. MED. 1230 (2009).

48 See, e.g., GUIDANCE FOR INDUSTRY: CLINICAL TRIAL ENDPOINTS, supra note 46.


50 Reimbursement is a significant concern; especially for drugs that may command high prices. But FDA is not part of that calculus; the most important agency for reimbursement decisions is the Centers for Medicare and Medicaid Services (CMS). CMS will occasionally allow reimbursement for treatments that do not demonstrate sufficient efficacy to meet FDA approval standards if there are no other options.

51 In fact, even an average user is not so “average” but rather a carefully controlled subject. Clinical investigations usually seek to control for behavioral, environmental and genetic variations. Of course, those variations may play a critical role in real world practice of medicine.

gave FDA authority to consider efficacy, the determination of individual efficacy was deemed to encroach too far on the physicians' purview of the practice of medicine.\(^{53}\)

Even in 1962, it was already clear that by creating a single drug designed to treat a whole population that suffers from a given condition, that there will be segments of the treated population that may suffer greater than average toxicities and get no benefit, segments of the population who may suffer greater than average toxicities and get benefit, segments that do not suffer toxicities but get no benefit, etc. \(^{54}\) For a drug to be approved, *most* people in the clinical trials must not suffer unacceptable toxicities and at least *some* must get significant benefit. But we know ahead of time that this will not be true of the whole population. Some—possibly many—may get no benefit at all. Others may suffer unpredictable toxicities. Congress recognized that possibility, but it was left to physicians to anticipate and deal with it.

While the decision to leave the question of individual treatment to a treating physician alone and block any role for FDA was political, it was also pragmatic. Although the concept of genetics certainly existed in 1962, the genetic code had not yet been “cracked.”\(^{55}\) Explanations of variation were crude science based mostly based on phenotypic evidence. Indeed, medicine itself was more of an art than a science. In that context, it made sense to leave the major decisions to a physician. There was relatively little information to know and the relationship with the patient yielded the most important information. Today, the relationship with the patient is still important, but the amount of information involved has exploded. This information includes individual genomes, human microbiomes, history of exposure to environmental agents, psychosocial and behavioral data.\(^{56}\) But that information comes with limited clinical guidance and often without validated tests.

Off-label use of drugs by physicians means that many drugs are used widely in the marketplace for conditions for which they are not approved by FDA. Recent studies seeking to document off-label use have found that off-label use may account for twenty percent of prescriptions written each year, many of which are for uses that are not well-documented, and include many drugs that carry a boxed warning.\(^{57}\) A drug that may be “safe” to treat a serious condition may not have a satisfactory risk–benefit balance for treating a less serious condition. Similarly, a recent analysis demonstrated that roughly thirty percent of common on-patent chemotherapies are used off-label. Of those, about one-third are used without conforming to National Comprehensive Cancer Network (NCCN) Drugs and Biologies Compendium recommendations.\(^{58}\) In situations lacking


\(^{54}\) Evans, Seven Pillars, supra note 52, at 501–03.

\(^{55}\) In 1944, scientists at Rockefeller University published an important paper that demonstrated that genes were composed of DNA. Watson and Crick published their epoch-making piece on the structure of DNA, the double helix, in 1953. But quick methods of genetic synthesis and analysis were not available until the 1980s and the human genome was first “mapped” in 2004. Leslie A. Pray, Discovery of DNA Structure and Function: Watson and Crick, 1 NATURE EDUC. 100 (2008), available at http://www.nature.com/scitable/topicpage/discovery-of-dna-structure-and-function-watson-397.

\(^{56}\) Nat’l Research Council, supra note 6, at 22.


\(^{58}\) Rena M. Conti et al., Prevalence of Off-Label Use and Spending in 2010 Among Patent-Protected Chemotherapies in a Population-Based Cohort of Medical Oncologists, 31 J. CLINICAL ONCOLOGY 1134 (2013). Lack of conformity to compendia should not necessarily be viewed as inappropriate use, especially
documented evidence of effectiveness, studies show that physicians often choose a drug approved for a clinically-related indication. For example, there is evidence of drugs approved for acute conditions being prescribed for chronic conditions. That makes intuitive sense, but it is not based on science and may be completely wrong—and it may ignore important potentials for toxicity.

Off-label prescribing is a double-edged sword. It allows physicians to adopt “new” products based on emerging science without waiting the years that proving a new indication might otherwise require. Similarly, it allows physicians to use drugs that are off-patent where there is little industry incentive to get approval for a new indication. It also provides access to treatments for individuals or small populations that might otherwise have no options. In this context, it is really physicians who are on the vanguard of personalized medicine, and the availability of off-label prescribing may be an important contributor to existing personalized medicine.

But physicians are making those decisions with extremely limited information. An essential part of FDA’s oversight of medical products is to require labeling that provides a physician “adequate directions for use.” But, especially when that use is not expected or widespread, neither FDA nor the drug sponsor can anticipate that use. Through guidance, FDA has encouraged the collection and use of pharmacogenomic data and “valid” biomarkers in drug labeling. Current estimates are that about ten percent of labels include that information. But it is not clear that that data is readily accessible or useful for many physicians. Physicians may not ever consider the actual label in making prescribing choices. There is evidence that sometimes physicians do not know that they are prescribing a product off-label. Even when they are aware, physicians are limited to the label information that will at most include information relating to the efficacy of the intended approved use and safety issues of the most known uses, and any information that they can glean from guidelines, medical literature and research data banks. Thus, not only do physicians not have access to the unknown

where the science is moving quickly. Moreover, FDA and the Compendia may use different standards for evidence. Id. Such use is expected by FDA. Food & Drug Admin., Guidance For Industry: IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer 4 (2004), available at http://www.fda.gov/cder/guidance/6036fnl.pdf (noting that oncologists often use approved drugs off-label after evaluating the published data and past clinical experience and that such use generally does not violate the FDCA).


Few physicians do any of this; even in an ideal situation, most physicians must rely on professional societies for recommendations. Emily A. Largent et al., Going Off-Label Without Venturing Off-Course: Evidence and Ethical Off-Label Prescribing, 169 JAMA Internal Med. 1745, 1746 (2009).
variabilities that remain undiscovered due to the constraints of our current approval process, they may not have access to some of the known variabilities that are known only to the sponsor (and FDA). That information often is considered confidential commercial information and FDA does not divulge it. The sponsor is unlikely to divulge it because it represents a significant part of its investment. Recently there have been legislative and regulatory initiatives requiring more data transparency. FDAAA requires that summary results from clinical trials used for approved drugs be published after approval. In 2013, FDA proposed releasing non-summary de-identified data that are pooled and masked so that they do not identify particular products. Some industry sponsors have taken steps to provide de-identified patient-level data from clinical trials to researchers for additional analysis. Others in industry strongly object to any such data sharing and have fought legislative attempts to require it. Even if the industry sponsor does release clinical data, it is not in a readily accessible form. Only a limited amount of such data is analyzed by independent researchers. Practicing physicians do not have the time, nor often the ability, to do the research that may be required. This puts physicians in an untenable situation (whether they realize it or not) because they bear all of the risk of these unknowns. Their patients, of course, bear the risk of the possible negative outcomes.

D. Access to Data is Severely Limited for Potential Drug-Developers

For many drug development companies, their accumulated data is the most valuable asset that they own. For some companies, the amount of such data is vast. It includes not just the data that a company may have submitted for a drug approval, but all of the failed research as well. It also includes tangential data, including large amounts of genomic and proteomic data that the company may have accumulated in the course of conducting clinical trials which may have ramifications for much unrelated research. When Myriad lost its patent case on the patentability of isolated genes in the Supreme Court in 2013, it continued to hold a much more valuable asset: the accumulated data acquired through more than a decade of testing related to mutations in the BRCA1 and BRCA2 genes that have been shown to be associated with hereditary breast—ovarian

67 There has of course been legal action and much discussion in the press and literature about legal constraints limiting pharmaceutical companies from providing information about off-label uses but regardless of the evolution of those rules, pharmaceutical companies only have the incentive to provide that information in situations where an off-label use will be widespread enough for it to have an economic incentive. As a result, there have also been new requirements in FDAAA for broader publication of clinical trial results. See infra text accompanying notes 77–79.


70 Thus far, GlaxoSmithKline, Johnson & Johnson, and Roche have released such data for independent research. See, e.g., Kevin Outterson, Clinical Trial Transparency—Antidote to Weaker Off-Label Promotion Rules?, 371 NEW ENG. J. MED. 1, 2 (2014); Switzerland’s Roche Pledges to Open Up Access to Drug Data, REUTERS (Feb. 27, 2013), http://www.reuters.com/article/2013/02/27/us-roche-data-access-idUSBRE91P0PK20130227.

71 Outterson, supra note 70.

72 Failed research can provide a significant competitive advantage because it means that a company can move forward in more fruitful directions while its competitors lose both time and money pursuing dead ends.

73 Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).
cancer syndrome. That data gave it, and continues to give it, an edge over potential competitors. And unlike patents, trade secret protection for data never expires. 74 It disappears only when those secrets are publicly revealed.

The FDCA prohibits FDA from revealing trade secrets revealed to it during the drug approval process. 75 FDA's definition of trade secret 76 is fairly broad and although an FDA task force recommended narrowing the definition in 2010, most scientific data remains protected by statute. 77 Since the late 1990s, however, greater transparency about clinical trials data has been demanded, principally because of potential safety issues like those that occurred with Vioxx. The Food and Drug Administration Modernization Act of 1997 (FDAMA) required the establishment of an online database, ClinicalTrials.gov, for public registration of clinical trials involving drugs designed for the treatment of serious and life threatening conditions. 78 FDAAA expanded those requirements in 2007 to include controlled clinical investigations, other than Phase 1 clinical investigations, of drugs subject to 21 U.S.C. § 355. 79 Although the European Medicines Agency (EMA) has announced that it will release de-identified patient-level data submitted after March 2014, 80 FDA continues to regard such data as commercial information and therefore entitled to confidentiality. 81 As noted earlier, 82 a number of companies have voluntarily begun to release de-identified patient data but many refuse to do so.

Like patents, the confidentiality of proprietary data promotes innovation, and many drug developers fear that the trend towards release of expanding amounts of proprietary data will limit innovation. 83 Others argue that access to expanding amounts of clinical trial data is precisely the boost that the increasingly beleaguered biopharmaceutical industry requires. 84 They argue that access to such data will aid the design of better subsequent clinical trials, permit the creation of comprehensive data bases across patient populations, and allow meta-analysis to sometimes substitute for additional clinical trials. 85 In addition, that information could aid reimbursement negotiations by providing data for comparative effectiveness; and finally, perhaps most important, the

74 But unlike patents, there is no federal remedy for trade secret infringement.
82 Outterson, supra note 70.
83 Principles for Responsible Clinical Trial Data Sharing, PhRMA (July 18, 2013), http://www.phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf.
85 Id. at 1578.
data would prevent developers from pursuing products and trials that are unlikely to succeed from the outset.\textsuperscript{86}

Unfortunately, it is likely that both arguments have merit depending on the context of the drug developer's business model and the products being generated. The Europeans are moving forward in requiring expansive transparency of clinical trials.\textsuperscript{87} FDA, to the extent permitted by statute, is moving in the same direction, albeit less comprehensively. This movement will likely hasten the separation of research and development and marketing functions in pharmaceutical companies. Pharmaceutical companies bear less risk and may have the potential to make more money by focusing on marketing alone. This may further reduce the drug pipeline. However, the full evolution, and whether such requirements enhance or impede innovation, is not yet clear.

Moreover, even such radical changes in transparency requirements are probably not sufficient for the full development of personalized medicine. Personalized medicine requires not just free access to clinical trial data but also patient experience data,\textsuperscript{88} combining claims and cost data, clinical data included in the electronic health record, and data reflecting patient behavior and preferences which may be commercially owned by entities outside the pharmaceutical and health provider industries. While data accessibility and coherence is a huge issue, bigger still is having sufficient analytics and methods to make what will be observational techniques sufficiently informative to allow for regulatory decision-making. FDA is clear that it seldom finds observational data sufficient for effectiveness determinations.\textsuperscript{89}

In addition, to be really useful, much of that data may need to be patient-identifiable. This raises new privacy issues. Although much of the required data is not covered by federal privacy laws applicable to health information, including HIPAA,\textsuperscript{90} these data still raise privacy issues for individuals. This is part of a larger question even than personalized medicine: how we can effectively use enormous amounts of networked data, "big data," without compromising individual desires and requirements. Meeting this goal will require new regulation and, often, new legislation.

\textsuperscript{86} Id.

\textsuperscript{87} See, e.g., Mello et al., supra note 81, at 1657 n.2 (European Federation of Pharmaceutical Industries and Associations jointly adopting the "Principles for Responsible Clinical Trial Data Sharing," a set of principles calling for biopharmaceutical companies to release more detailed clinical trial data).

\textsuperscript{88} FDA is gathering increasing amounts of patient-reported outcomes (PROs) pursuant to Food and Drug Administration Safety and Innovation Act (FDASIA) requirements for patient perspectives in the benefit-risk calculus. See Stephanie Beasley, Woodcock: Legislation Not Needed for Patient-Reported Outcomes Collection, 20 INSIDEHEALTHPOLICY.COM'S FDA WEEK 29 (2014), available at http://search.proquest.com/docview/1545796840. But this endeavor is a relatively modest one compared to what would be required for full realization of personalized medicine.


IV. CURRENT FOCI FOR SOLUTIONS TO PROBLEMS IN REALIZING PERSONALIZED MEDICINE

A. Validation of Genetic Tests

FDA is not blind to the obstacles surrounding effective and supportive regulation of personalized medicine. It has encouraged increased use of pharmacogenomic data in general product submissions.\(^9\) In 2004, FDA launched the Critical Path Initiative\(^2\) which was designed at least partially to develop better avenues to true personalized medicine. Funding for that program has been spotty at best, and much of its work appears to have plateaued, but through it and other initiatives FDA has made a major push to deal with companion diagnostics.\(^9\) As the FDA Commissioner has herself noted, the success of personalized medicine depends on the availability of valid companion diagnostic tests.\(^4\) Increasing this availability has been FDA’s primary focus in this area over the last decade.

There have been two major obstacles to this task. The first, largely institutional and more easily resolvable, is that companion diagnostics require two FDA centers to work together. For a simple example, the drug would be subject to review by the Center for Drug Evaluation and Research (CDER) while the genetic test is typically regarded as a device and is subject to review by the Center for Devices and Radiological Health (CDRH). In this case, CDRH has the technical expertise, but CDER has the experience necessary for the decision of whether the test is an appropriate diagnostic to be used with the drug. Working together is essential. As mentioned, this obstacle of multi-center review is more easily resolvable, and in recent years, FDA has become accustomed to dealing across centers and has developed mechanisms for this type of review. More tricky may well be getting drug developers to bring all the necessary pieces to review from the beginning of the development process.\(^5\)

This second obstacle is more difficult because it involves a somewhat contentious issue of FDA’s legal authority. Many of the genetic tests currently used as companion diagnostics are laboratory developed tests (LDTs) which are arguably not products\(^1\). See, e.g., FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSIONS (2005), available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126957.pdf.


\(^4\) See, for example, the Voluntary Exploratory Data Submissions program, introduced in 2004, which facilitates companies sharing genetic and other biologic information related to their therapeutic agents outside of the formal regulatory submission process. Voluntary Exploratory Data Submissions (VXDS), FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083673.htm (last updated Oct. 25, 2011); see also FOOD & DRUG ADMIN., IN VITRO COMPANION DIAGNOSTIC DEVICES, supra note 3; FOOD & DRUG ADMIN., DRIVING BIOMEDICAL INNOVATION: INITIATIVES TO IMPROVE PRODUCTS FOR PATIENTS (2011), available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm274333.htm.

but services and therefore not subject to FDA’s jurisdiction. FDA’s way around this problem has been to require that LDTs used to support a drug approval must be either cleared through a 510(k) process or approved as a PMA. Thus FDA argues that, in essence, the LDT becomes a medical device and is therefore a product subject to its jurisdiction. Thus far, this interpretation has not been tested in the courts.

Because of their importance to the use of the drug and therefore relative risk, FDA would prefer that most companion diagnostics go through a PMA process rather than the abbreviated 510K process. Of the twenty-one companion diagnostic IVDs that FDA has approved or cleared, twenty were reviewed through a PMA process, and one was reviewed de novo and classified and subsequently cleared as a Class II device. But FDA has also recognized that the longer PMA process stands as an obstacle to the development of appropriate tests and it has established a modular PMA process that streamlines the process. In addition, clinical validity does not mean utility, and FDA is ill positioned to make evaluations on that score because it does not regulate the practice of medicine and is not responsible for reimbursement decisions. Most clinical utility decisions are made outside FDA. FDA will have to develop methods to coordinate with many other institutions.

B. Orphan Drug Program—“We are all orphans now”

It is sometimes argued that the orphan drug program may provide an appropriate pathway for personalized medicine. On first glance, that argument has merit. The orphan drug program is designed to be more nimble than the ordinary drug approval process and FDA has entertained considerable flexibility in the process. By the 1970s, it was recognized that the potentially long and expensive approval process was a major obstacle to the development of drugs to treat rare diseases because the sponsor could not hope to recoup its development expenses in the marketing of the drug.

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98 21 C.F.R. § 814.20.
100 List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools), FOOD & DRUG ADMIN., http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm (last updated Dec. 23, 2014).
102 While FDA is often responsible for determining clinical validity, determination of utility is typically the province of providers (and clinical guideline developers) and payers. ROUND TABLE ON TRANSLATING GENOMIC-BASED RESEARCH FOR HEALTH, INST. OF MED., GENOME-BASED DIAGNOSTICS: DEMONSTRATING CLINICAL UTILITY IN ONCOLOGY 11–27 (Adam C. Berger & Steve Olson eds., 2013). CDC has conducted the EGAPP program; CMS and AHRQ are studying clinical utility more systematically. The larger health insurers are also weighing in on these decisions.
rare diseases or conditions are defined as affecting fewer than 200,000 people in the United States.\textsuperscript{106} So, in the 1980s, Congress passed legislation to create incentives for the development of such drugs.\textsuperscript{107} Sponsors developing drugs for such conditions are eligible for tax credits and extended exclusivity periods.\textsuperscript{108}

By most accounts, the orphan drug program is a success. More than 400 drugs have attained FDA approval through the program,\textsuperscript{109} and many more are in the pipeline.\textsuperscript{110} Patient-advocates associated with rare disease groups generally believe that the program has made new drugs available for rare diseases that would not have been available otherwise.\textsuperscript{111} In some ways, the program seems tailor-made for personalized medicine, because one of the major obstacles for developing such therapies is that the populations are so small that there are insufficient incentives for drug companies to develop individualized treatments. In addition, FDA regulations require FDA to use its scientific judgment to exercise flexibility in determining the kind and quantity of data and information required to meet the statutory standards for approval,\textsuperscript{112} and FDA has shown particular willingness to exercise this flexibility within the context of orphan drugs.\textsuperscript{113} Many of those drugs were tested using very few subjects, in investigations tailored to the unique context of the condition involved, and in a relatively short period of time, without sacrificing the scientific rigor required for approval.\textsuperscript{114} This seems to be exactly the flexibility and nimbleness that personalized medicine requires.

However, the program has also been "gamed" significantly. There is evidence that the orphan drug program is useful for drug sponsors "seeking a disease" for an existing compound.\textsuperscript{115} More importantly, there is evidence the drug sponsors often choose a secondary indication that meets orphan drug requirements when a different or broader indication is their real goal.\textsuperscript{116} This is a direct negative consequence of the use of phenotypic disease indications. If pathophysiologic indications were used instead, a number of these drugs would not qualify for orphan status because the relevant population would exceed the statutory limit. Many of these drugs may become blockbusters; at least 9% of orphan drugs have reached blockbuster status and 25 orphan drugs have annual sales exceeding $100 million.\textsuperscript{117} The worldwide orphan drug market

\textsuperscript{106}See, e.g., Sasinowski, supra note 104.


\textsuperscript{108}See statutes cited supra note 107.

\textsuperscript{109}Developing Products for Rare Diseases & Conditions, FOOD & DRUG ADMIN., http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm (last updated Feb. 26, 2015).


\textsuperscript{111}See Marlene E. Haffner, Adopting Orphan Drugs—Two Dozen Years of Treating Rare Diseases, 354 NEW ENG. J. MED. 445, 445 (2006). The Broader Availability of Treatments Is Praised, but the High Cost of Many of These Treatments Remains a Problem.

\textsuperscript{112}21 C.F.R. § 314.105(c) (2015); see also Sasinowski, supra note 104.

\textsuperscript{113}Id.

\textsuperscript{114}Id.


\textsuperscript{116}Id. at 225.

\textsuperscript{117}Id. at 216, 223.
is set to reach $127 billion by 2018, accounting for nearly 16% of total prescription drug sales.\textsuperscript{118}

The significance of the orphan drug program for the economics of the pharmaceutical industry can be demonstrated by the protracted battle between the main lobbying organization for the pharmaceutical industry, Pharmaceutical Research and Manufacturers of America (PhRMA), and the U.S. agency that provides drug discounts to certain supported entities, the Department of Health and Human Services (HHS) Health Resources and Services Administration (HRSA) over so-called 340b reimbursement. One of the attractions of orphan drugs for developers is that orphan drugs are excluded from mandatory discounting that HRSA imposes on drugs sold to HRSA-supported health centers, Ryan White clinics and State AIDS Drug Assistance programs, Medicare/Medicaid Disproportionate Share Hospitals, children’s hospitals, and other safety net providers.\textsuperscript{119} But HRSA has interpreted the statute to exclude sales of orphan drugs for non-orphan indications.\textsuperscript{120} PhRMA has fiercely fought that interpretation—with good reason. Sales of orphan drugs for non-orphan indications represent a significant portion of the highly lucrative orphan drug market.

However, the biggest issue for our purposes is that the orphan drug program is based on the existing paradigm that focuses on homogeneity rather than variation. A central tenet of personalized medicine is that all diseases and conditions will have variation and all variation should have treatment. The orphan drug program assumes that variation is rare, not common. Yet personalized medicine reveals the falsity of that proposition. Already the National Institutes of Health (NIH) reports that nearly 7,000 rare diseases affect more than 25 million Americans and their families.\textsuperscript{121} Approximately 80% of rare diseases are genetic in origin.\textsuperscript{122} As genomic and molecular medicine progress more and more people will be determined to have rare variants; some of those variants will be actionable. While many of these variants will not be causal for a rare disease, many of them may affect an individual’s care or treatment. More and more people will be found to have uncommon responses to common diseases or uncommon responses to broadly prescribed drugs. The orphan drug program does not address those needs.\textsuperscript{123} We are all orphans now.

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\textsuperscript{118} Carly Helfand, \textit{Top 20 Orphan Drugs By 2018}, \textsc{FiercePharma} (July 23, 2013), http://www.fiercepharma.com/special-reports/top-20-orphan-drugs-2018.


\textsuperscript{122} Inst. of Med., \textsc{Rare Diseases and Orphan Products} 52 (Marilyn J. Field & Thomas F. Boat eds., 2010).

\textsuperscript{123} For example, the National Cancer Institute has recently launched an “exceptional responders program” exploring patients who experience a response to an otherwise failed drug trial. Torna Ray, NCI Initiates Effort to Sequence, Collect Outlier Drug Responses, Inform Personalized Approaches, GenomeWeb (Oct. 1, 2014), https://www.genomeweb.com/clinical-genomics/nci-initiates-effort-sequence-collect-outlier-drug-responses-inform-personalized.
C. Post-Approval Monitoring and Progressive Licensing Schemes

Some of the most creative and pragmatic approaches to encouraging the development of personalized medicine focus on post-market activity. Traditionally, other than collecting adverse event information and mandating occasional label changes, FDA had little to do with a drug once approved. FDA lacked explicit authority to require post-market clinical trials. Vioxx changed that; Congress moved to provide FDA new powers with FDAAA in 2007. If, during or after the approval process, a drug poses known risks, or there are signals of the potential for serious risk, FDAAA gives FDA the power to require labeling changes or additional post-market study. But FDA has interpreted that to mean that it cannot order further study on questions of effectiveness, just on potential safety issues. At least one scholar has challenged that interpretation. Barbara Evans argues that lack of response is a safety issue as well as an efficacy issue and therefore FDA has the power to order additional study including additional pharmacogenomic tests. Further, she argues that this safety issue gives FDA full power to generally require drug sponsors to address heterogeneity of treatment effects in approved drugs. Evans’s argument is very controversial and would likely be strongly opposed by industry and possibly by FDA. It is also necessarily post hoc. It does little to encourage industry to address heterogeneity in the original design of the product.

Law professors Shannon Gibson and Trudo Lemmens also argue for enhanced post-market review—or perhaps even better, a scheme of progressive licensing. They point out that the narrow population base for what they call “niche market therapies” limits the data that can be gathered in a reasonable pre-approval process and that post-approval study is necessary to gather sufficient data to truly assess efficacy and safety endpoints. In addition, they call for greater industry transparency to allow for more informed off-label and on-label use by practitioners. Their scheme has the advantage

124 FDA did impose post-approval commitments on sponsors, but their compliance was at least theoretically voluntary. Of course, since FDA always had the power to withdraw approval, even pre-FDAAA, FDA had de facto power to pressure sponsors for such commitments. However, where risks were real but not so severe as to warrant withdrawal of approval, FDA’s power was significantly diminished. See Daniel Carpenter, Policy Forum: Reputation, Gatekeeping and the Politics of Post-Marketing Drug Regulation, 8 VIRTUAL MENTOR 403, 404 (2006) (Virtual Mentor is now called the AMA Journal of Ethics). FDA did have statutory authority to require pediatric studies. The Pediatric Research Equity Act (PREA), 21 U.S.C. § 355a (2012), is a 2007 legislative successor to FDA’s 1998 Pediatric Rule. The Pediatric Rule is codified at 21 C.F.R. §§ 314.55 and 601.27, with additional amendments to 21 C.F.R. §§ 201, 312, 314, and 601. PREA allows FDA to require additional pediatric studies for approved drugs that are used widely with children.

125 FDAAA § 901(b), 21 U.S.C. § 355(o) (2012). Section 505(o) of the FDCA authorizes FDA to require certain postmarketing studies or clinical trials for prescription drug and biological products approved under section 505(b) of the FDCA or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. § 262).


127 Evans, supra note 18.

128 Id. at 7–8.


130 Id. For now, that transparency is resisted by large swathes of industry.
of allowing a potential product to enter the market more quickly thus addressing the need for greater nimbleness within personalized medicine. But once again, this scheme is post hoc, it speaks to some of the problems in regulating personalized medicine but not many of the problems inherent in the development of the products in the first place. It is certainly better than current practice, but far from ideal.

D. Regulation of the Practice of Medicine

One solution for the "black box" medicine created by the lack of transparency in data in drug development is to allow greater communication between drug sponsors and physicians about potential off-label use. This solution is, of course, very much in the news, especially since the Caronia decision in which the United States Court of Appeals for the Second Circuit ruled that the government does not have the authority to prohibit pharmaceutical company representatives from making truthful claims about the potential off-label uses of drugs. For our purposes, however, the First Amendment legal issues are not the primary concern but whether such a solution promotes better off-label use. Even that is extremely controversial. Proponents of allowing drug sponsors to disseminate more information about off-label uses argue that it provides the best opportunity to educate physicians by the party with the most complete information. Opponents argue that such education would amount to promotion and that it would limit drug sponsors' incentives to seek approval for new indications. Likely both views have significant merit. The critical questions are whether that education would be sufficient to make a difference and whether the potential promotion of off-label use would do more harm than good. Those questions deserve further study, but even under the best of circumstances physicians' understanding of drugs mechanisms of action will be limited.

Another solution is to restrict off-label use. Until recently, such a solution would have been almost heretical, but there have recently been inroads in the unfettered physicians' right to use approved medical products in any way that they see fit. As noted earlier, FDA prescription regulation is focused on the idea that a label can be devised that provides physicians adequate directions for use. If the average physician is unlikely to have the information, means or experience to use a specific product, then perhaps its use can be restricted. In 2007, FDAAA introduced potentially far-reaching limits on the practice of medicine doctrine allowing FDA to impose restrictions (e.g. place and mode of use) on approved drugs "to assure safe use of the drug, because of its inherent toxicity or potential harmfulness." France has recently introduced comprehensive new rules on off-label use because of the increasing complexity of medical products.

But although physicians are perhaps less vociferously protective of their rights under the practice of medicine doctrine than in decades past, there are segments of that group that will not accept significant limitations without a fight. And they will find plenty of

131 United States v. Caronia, 703 F.3d 149, 162 (2d Cir. 2012).
support in the FDCA, its legislative and subsequent history. For example, Section 214 of FDAMA explicitly acknowledges the practice of medicine doctrine in the context of medical devices. It prohibits FDA from interfering with the authority of a health care practitioner to prescribe or administer any legally marketed device for any condition or disease within a legitimate practitioner-patient relationship.

Most important, limiting physician off-label prescribing authority only eliminates the problem of potential physician practice issues, it does not supplement it with alternative guidance and means of access. Our whole medical product regulatory scheme has long depended on the physician as learned intermediary, bringing together useful but potentially dangerous products and patients who need them. Limiting physician activity, without providing other means of making those links, potentially leaves patients without useful treatments.

E. Repositioning or Repurposing Drugs

One of the most promising new directions for drug development that may affect personalized medicine is in the area of drug repurposing—new uses for old drugs. This involves both drugs that have been approved for other purposes and drugs that failed to gain approval when first developed for some other indication. But its full potential cannot be realized without major regulatory changes. These include having the drug approval process require study that goes beyond the effect of the drug on a disease process to better understanding the physiological mechanisms that are in play. Moreover, the data from one approval needs to be made more useful for other potential indication and to account for variation among individuals. Potential additional uses for drugs can be revealed efficiently only by understanding these pathophysiological factors. This also requires increased data access since sharing much of this data is not currently required. In addition, the patent implications of much of this work is unclear; thus changes may be required in the patent rules.

Repurposing, of course, is not new. Some people even consider off-label use to be a method of repurposing drugs. But "true" drug repurposing involves developing new labeling for existing approved drugs and new indications for chemical (or biologics) entities that have undergone some testing but have not met safety or efficacy requirements for approval. This may be done by the pioneer developer alone, more often in collaboration with academic medicine or others, and sometimes by developers that have no relationships at all with the original developer. When the pioneer developer is not the sponsor, approval is sought under section 505(b)(2) which offers a sort of

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137 Wang & Zhang, supra note 38; see also Philippe Sanseau et al., Use of Genome-Wide Association Studies for Drug Repositioning, 30 NATURE BIOTECHNOLOGY 317 (2012).


139 A potentially exciting example of this is the discovery by Stanford researchers using a bioinformatics approach to study large numbers of drugs that the now rarely used tricyclic antidepressants might be potential treatments for human small cell lung cancer and other neuroendocrine tumors. Nadine S. Jahchan et al., A Drug Repositioning Approach Identifies Tricyclic Antidepressants as Inhibitors of Small Cell Lung Cancer and Other Neuroendocrine Tumors, 3 CANCER DISCOVERY 1364 (2013).

hybrid pathway allowing the sponsor to use information in published literature reports and/or FDA’s findings of safety and/or effectiveness for one or more listed drugs in its application for approval. The benefit of repurposing is that since both FDA and scientists already have some experience with the drug, there may be less investment risk in pursuing approval and the approval process can often be much shorter and less expensive. Furthermore, the additional clinical testing and labeling that may be required provides physicians much better data about efficacy and use of the product than is available through off-label prescribing and reimbursement may be more likely. The downside of repurposing is that it may involve complicated patent scenarios, particularly when the original pioneer developer is not involved. In addition, 505(b)(2) applicants may only qualify for three years of exclusivity for the new indication. In such cases, developing an entirely new drug may look more profitable. Because of the limited profit potential, this is perhaps a good reason for this to be done through collaborations by government, academia, provider groups and industry rather than by industry alone. Nonetheless, one remarkably successful example of drug repurposing is Celgene’s repurposing of thalidomide, which was originally marketed as a sedative, for leprosy and multiple myeloma and later for other cancers. By fully understanding the pathophysiologic properties of the drug, Celgene was able to develop new intellectual property and become one of the most profitable companies in the industry.

The National Institutes of Health’s National Center for Advancing Translational Sciences (NCATS) has created a collaborative program between pharmaceutical companies and academic medical centers: “Discovering New Therapeutic Uses for Existing Molecules” which is designed to facilitate increased repurposing. FDA has also created a database that facilitates repurposing of drugs for rare diseases using publicly available information but still information that would not be readily accessible for potential developers. But these two programs, which demonstrate considerable promise, represent only a fraction of what might be possible with effective and efficient repurposing. There is significant evidence that new bioinformatics methods such as text


142 See Sem, supra note 136, at 151–60.


144 Thalidomide is perhaps best known as the notorious drug that caused horrific birth defects in the late 1950s. See, e.g., Kenneth C. Anderson, Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine, 7 Nature Med. 275 (2001) (reviewing Rock Brinser & Trent Stephens, Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine (2001)). Of course, thalidomide was prescribed in the 1950s in Europe based on its phenotypic effect. Had its mechanism of action been even partially understood, these birth defects might have been avoided.


146 Discovering New Therapeutic Uses for Existing Molecules, Nat’l Insts. of Health, http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html (last visited Dec. 10, 2014). This program is fairly constrained as the pharmaceutical industry has had limited interest in pursuing collaborations that might involve drugs that have short patent terms remaining. Sem, supra note 136, at 150. In fact, the NCATS pilot actually involved compounds that have not yet been approved as drugs. Beachy et al., supra note 145, at 40.

mining, chemical genetics and network analysis afford ample opportunities for drug repurposing for personalized medicine. Until recently, repurposing opportunities were discovered largely serendipitously by systematically testing drugs against targets. But now, by gathering huge amounts of data, scientists can identify new, less obvious targets and do so far more efficiently. But creating the data infrastructure and regulatory pathways to make this systematic is still elusive. Since FDA has limited power to require standardized clinical testing, existing data relating to a repurposing drug candidate may be difficult to use for a different purpose. That may be especially true for a drug that was approved some time ago. While there is now a tremendous amount of public data available, and new resources in electronic health records, none of that data is easy to coordinate. Nor is it clear how FDA will assess that data in the drug approval process. There are still gaps created because of the trade secret value of data held by industry (and even academic centers and other commercial entities.) Finally, there is, as with all big data in the biomedical sphere, a paradox that will be difficult to bridge. Efficient repurposing requires large data sets and data collaboration; this will be all the more true for repurposing designed for personalized products. But sharing and coordinating data also limits potential exclusivity thus possibly dampening investment interest.

F. Adaptive Trials

As discussed earlier, the FDCA requires “substantial” evidence of effectiveness under the conditions of use in order for a new drug to be approved. This has usually meant at least two randomized controlled trials (RCTs), the “gold standard” of clinical investigation. In recent years, however, FDA has allowed increased flexibility in the characteristics of the RCTs required and there has been considerable evolution in clinical trial design. For personalized medicine, one of the most exciting of these is the development of the adaptive clinical trial.

Adaptive clinical trials have been described as “learn as you go trials.” Both diagnostic tests and treatments may evolve as the trial progresses. Rather than dropping out, a subject who fails with one investigative treatment may move on to another. Drugs and dosing may be adjusted for individual needs based on individualized diagnostic criteria. Endpoints typically tie specific diagnostic biomarker signatures to efficacy data for a particular regimen. Data from the whole trial is gathered throughout and adjustments are made according to the data. Rather than treating the study population as a homogeneous whole, careful attention is paid to subgroups who may be responding differently to treatment. This allows participants in the trial to receive largely personalized treatment, a far different scenario than the usual RCT which might even

148 Jin & Wong, supra note 138.
149 BEACHY ET AL., supra note 145, at 17–29.
151 This has been FDA’s position since the FDCA included efficacy requirements for approval. DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 354–56 (2010); 21 C.F.R. § 314.126 (2015).
152 Other innovations such as “pragmatic clinical trials” or “large simple trials” which test products under real world contexts are becoming increasingly important for comparative effectiveness data and may eventually play a larger role in personalized medicine. Observational studies may also contribute important data, but FDA is still reluctant to base an approval on observational data. ROUNDTABLE ON TRANSLATING GENOMIC-BASED RESEARCH FOR HEALTH, supra note 102, at 36.
153 Id.
involve sub-optimal individual treatment, and different from usual clinical care where new experimental therapies are out of reach.

One of the best examples of an adaptive trial is the I-SPY breast cancer trial. Breast cancer is an ideal subject matter because the science is advanced and it is well known that there are many different sub-types within the overall breast cancer diagnosis. Designed for women with aggressive cancers with uncertain treatment pathways, the I-SPY trials have involved more than twenty collaborating cancer centers, FDA, NIH and a number of pharmaceutical companies. Funding mostly comes from non-profit foundations.

Adaptive clinical trials are an exciting method, but they are very hard to do and their overall design is still a work in progress. They require very experienced researchers, large numbers of participants, sophisticated bioinformatics, cooperation and collaboration between multiple pharmaceutical companies and the researchers and frequent FDA consultation. In an ideal world, this may be the future of personalized medicine—where not just research but any unusual clinical care is offered. For now, however, only certain specialties like breast oncology have the sophistication, organization and resources to accomplish such a trial.

Since the FDCA affords FDA flexibility in clinical trial design, FDA has considerable leeway in providing guidance for adaptive clinical design. In 2010, it provided a draft guidance: “Adaptive Design Clinical Trials for Drugs and Biologics,” and FDA has been working with PHRMA and its European counterparts to develop further guidance. Because biomarkers play such a crucial role in adaptive trials, many of the issues relating to biomarker validation play a role here as well. And once again, FDA has to grapple with large quantities of data and proper assessment of that data. While very promising, adaptive clinical trials are a only in the early stages of development. Their full effect as a route to personalized medicine remains to be seen.

V. ADDITIONAL REQUIREMENTS FOR FULL REALIZATION OF PERSONALIZED MEDICINE

As the foregoing discussion demonstrates, FDA and other stakeholders have creatively worked within current constraints to develop personalized medicine. But full realization of personalized medicine will require much more. The crucial element needed for true personalized medicine is data. As described in Part III, networked medicine, a prerequisite for personalized medicine, requires huge amounts of data from multiple sectors including sectors outside the traditional health-related spheres. It is unlikely

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154 Now planning its third iteration as I-SPY-3; I-SPY-1 is complete and I-SPY-2 beginning to wind up. See Food & Drug Admin., Paving the Way for Personalized Medicine, supra note 25, at 46; AD Barker et al., I-SPY2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy, 86 Clinical Pharmacology & Therapeutics 97 (2009).


157 Another example of adaptive design is the BATTLE trial for non-small cell lung cancer; see Donald A. Berry, Roy S. Herbst & Eric H. Rubin, Reports from the 2010 Clinical and Translational Cancer Research Think Tank Meeting: Design Strategies for Personalized Therapy Trials, 18 Clinical Cancer Res. 638 (2012).


159 See supra text accompanying notes 63–64.
that FDA can or should play the dominant role in the acquisition and banking of such
data.\textsuperscript{160} FDA’s role is to administer the accumulation of data from the clinical trials
that it oversees and the determination of how to acquire and use data from all sources
in the drug approval process. FDA will have to continue to manage confidentiality
concerns where data is proprietary. It is not yet clear how FDA will value such data,
what additional studies it might require and what it will do with data that might be
actionable but difficult to prove. Considerable guidance will be required. But even that
somewhat more constrained role will be difficult to achieve.

It is likely that data from clinical trials will continue to become more transparent.
But for that data to be truly useful, FDA will need to be given greater power over the
design and standardization of the overall clinical trial process. As noted earlier, FDA
has limited authority to demand research that goes beyond the indication sought for
any drug approval. It has no authority to demand full exploration of the full breadth of
the pathophysiologic aspects of an investigational drug’s action.\textsuperscript{161} In fact, even within
the confines of a given indication, FDA can recommend clinical trial design, but it does
not have the authority to demand it.\textsuperscript{162}

One way to imagine the requirements of personalized medicine is to imagine building
blocks. Those blocks need to be able to connect to each other solidly. If they do, you
can keep adding on as new blocks are acquired. If they don’t, you have to start the
building anew each time. Our current drug approval process is more like the latter. Each
investigational drug comes to FDA as a separate product largely distinct from products
that have come before it and those that might follow it. The FDCA does not incentivize
processes that might be used to allow greater coordination and collaboration that might
allow current drug approvals to be built upon easily in the future by more personalized
products. In fact, intellectual property interests likely push in the opposite direction. As
a result, the development process must often begin anew each time. Related research
may not be included or even known. And the wheels of the approval process also move
too slowly for personalized medicine. Even the relatively nimble section 505(b)(2)
process takes years, not months, to produce a product approval.

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration
Act, better known as “Hatch-Waxman,”\textsuperscript{163} which created a pathway for approval of
generic drugs. It is likely that similar legislation is needed for personalized medicine.
That legislation needs to provide FDA new powers to require standardization, greater
exploration of the full pathophysiologic characteristics of drugs and to promote
innovation through data transparency. Like Hatch-Waxman, it will also need to find

\textsuperscript{160}Exactly what entity or entities should take on that role is a question outside the scope of this article
since such uses of big data affect all aspects of medicine and health promotion. See, e.g., \textsc{William W. Lowrance},
\textsc{Privacy, Confidentiality, and Health Research} (2012); \textsc{Nat’l Research Council, Expanding Access to
Research Data: Reconciling Risks and Opportunities} (2005); \textsc{Robert M. Hauser et al., Nat’l Research
Council, Conducting Biosocial Surveys: Collecting, Storing, Accessing, and Protecting Biospecimens
and Biodata} (2010); \textsc{Nat’l Research Council, Proposed Revisions to the Common Rule for the Protection
of Human Subjects in the Behavioral and Social Sciences} (2014); \textsc{Martin Hilbert & Priscila Lopez, The
World’s Technological Capacity to Store, Communicate, and Compute Information, 332 Science 60 (2011)}.

\textsuperscript{161}See \textsc{Garret A. FitzGerald, Testing Cardiovascular Drug Safety and Efficacy in Randomized Trials,
114 Circulation Res. 1156, 1160 (2014) (calling on FDA to take on such a role, but it is clearly outside FDA’s
current authority)}.

\textsuperscript{162}21 C.F.R. § 312.41 (2015); see Steven Woloshin et al., \textsc{US Food and Drug Administration and Design
of Drug Approval Studies, 312 JAMA 2163, 2163 (2014)}.

(codified as amended in Chapter 9 of 21 U.S.C).
a path to foster incentives for development or FDA will have new powers but few products to approve.

VI. CONCLUSION

It seems more and more that the needs of personalized medicine will stretch FDA's authority under FDCA to the breaking point. Nonetheless, with a trillion dollar industry with multiple stakeholders, wholesale restructuring of the FDCA seems unlikely. But two emerging trends may push industry to seek major changes in the way product development takes place. One of these is the increasing speed and accuracy and reduced cost of next generation genetic sequencing and whole genome sequencing. Increasing availability of those technologies will move personalized medicine more into truly individualized health care thus changing the types of products and treatments that will be offered in the marketplace. Simultaneously, industry, particularly the pharmaceutical industry, is limiting its R&D budgets and focusing more on product delivery than product development. This may change industry's perception of investment value and consequently its protection of its intellectual property. Currently, industry has resisted calls for greater transparency in its drug development because that information is its real investment value. But greater availability of whole genome sequencing is likely to call into question the ownership of much of that information. If these trends push industry to greater sharing of intellectual property, and something like open source modular development becomes a reality, that would indeed require restructuring of the FDCA. And it may even be politically possible because the initiative will not be coming from government but from the marketplace. Time will tell. What does seem certain is that personalized medicine will require FDA to undertake significant regulatory changes if it is to be a relevant and effective gatekeeper. Its ability to do so will likely be impeded by limits on its legal authority. It remains to be seen whether Congress will give it any help.