Administrative Law & Regulation

Free To Choose Medicine

By Gregory Conko and Bartley J. Madden***

Note from the Editor:

This article is about the Free To Choose Medicine concept. As always, the Federalist Society takes no position on particular legal or public policy initiatives. Any expressions of opinion are those of the authors. The Federalist Society seeks to further discussion about the Free To Choose Medicine proposal and FDA regulation. To this end, we offer links below to different perspectives on the issue, and we invite responses from our audience. To join this debate, please email us at info@fed-soc.org.

Related Links:

- Development & Approval Process (Drugs), Food and Drug Administration: http://www.fda.gov/drugs/developmentapprovalprocess/
- Susan Thaul, How FDA Approves Drugs and Regulates Their Safety and Effectiveness, Congressional Research Service (2012): http://www.fas.org/sgp/crs/misc/R41983.pdf
- Philip Hilts, The Agency We Need: Defending the FDA, PBS Frontline Interview: http://www.pbs.org/wgbh/pages/frontline/shows/prescription/defending/
- The Future of Drug Safety: Promoting and Protecting the Health of the Public, Institute of Medicine (2006): http://www.iom.edu/Reports/2006/The-Future-of-Drug-Safety-Promoting-and-Protecting-the-Health-of-the-Public.aspx

Introduction

The U.S. Food and Drug Administration approved 39 new medicines in 2012, the largest number in 16 years.[1] Some, including the agency itself, are proclaiming a new era of cooperation and productivity for the pharmaceutical industry and the FDA.[2] But a closer look at what's happening in the industry reveals deep problems. Development costs are rising, research pipelines are drying up, and as medical science targets more complex diseases such as cancer and Alzheimer's, it has become increasingly more difficult to translate basic scientific discoveries into marketable products that work well in the clinic.

The challenges facing the pharmaceutical industry are not merely technical, however.

In response to high-profile safety issues associated with such drugs as Vioxx[3] and Avandia,[4] the FDA has raised the stringency of its new product reviews, and various manufacturers have reported increasing uncertainty regarding how the agency will evaluate the safety and efficacy of new drugs and medical devices.[5] FDA demands for more and more data to provide greater and greater confidence in its decision making has caused the length of clinical trials to grow[6] and the median number of tests conducted per patient (such as routine exams, blood tests, and x-rays) to rise.[7] These new hurdles have also made it more difficult to enroll patients in trials and to keep them in the trials until completion.[8]

FDA demands for stronger evidence of drug effectiveness, tightening concerns about rare but serious side effects, and uncertainty regarding which drugs might ultimately meet the agency's shifting approval standards has caused many manufacturers to abandon projects long before a New Drug Application is even submitted.[9] As science journalist Malorye Allison explained in the journal *Nature Biotechnology*, "The expanding timelines, size, failure rate and cost of trials have finally reached a point where, like the towering US debt, nobody can pretend it is viable."[10]

The FDA has undertaken efforts to rethink its clinical trial model in recent years.[11] But even these changes remain plagued by the agency's tunnel vision focus on generating the statistically "cleanest" dataset on which to base its approval or disapproval determinations. The FDA's preoccupation with safety is, to some extent, commendable. But there is no doubt that it raises costs, prolongs development times, and restricts the number of new medicines brought to market. These too are important system-wide goals of the drug development, testing, and commercialization process that FDA's existing regime all but ignores.

From systems analysis we learn that any proposed improvement should be judged in terms of achieving the overall system goal rather than a gain in the local efficiency of any particular component of the system.[12] Applying systems thinking to the FDA reveals that the invalid assumption that safety and efficacy are the only things that matter has caused the agency to demand extraordinarily expensive clinical trials (measured in both time and money) in order to improve its statistical analyses. But an unintended effect has been degradation in achieving the system goal of delivering better drugs to patients, sooner, and at lower cost.

**Executive Director and Senior Fellow at the Competitive Enterprise Institute*

***Senior Fellow at the National Center for Policy Analysis (NCPA) and author of* Free To Choose Medicine: Better Drugs Sooner at Lower Cost, *available at Amazon.com*: http://www.amazon.com/Free-To-Choose-Medicine-Better/dp/0988596903/ref=pd_sim_sbs_b_1.

At the same time, the FDA's monopoly control over drug testing and marketing denies millions of patients the freedom to choose a treatment that does not meet the agency's gold standard for approval. Both FDA and Congress demand that the public accept without question the agency's role in ensuring "safe and effective drugs." But no drug is 100 percent safe. At best, the FDA can merely make a judgment call that the benefits of the drugs it approves outweigh the expected risks. The amount of risk a patient is willing to tolerate will vary widely from patient to patient, however. Some will want the agency to proceed at a slow and deliberate pace, while others demand earlier access, even if that comes with attendant uncertainty and the risk of harm. After all, life threatening and severely disabling diseases come with their own, quite substantial risks.

Ultimately, neither Congress nor the FDA can know what the optimal risk/benefit balance is, even for the average patient. What matters for individual patients is the opportunity to choose a medical treatment that meets their unique health status and risk tolerance. And though the FDA's judgment will be important for some patients, it will not be the only consideration, nor even the most important, for millions of others. What is needed, therefore, is not just tinkering with the FDA's standard clinical testing and approval model, but a completely different alternative that provides patients with greater choice, while promoting an overall system goal of better drugs, sooner, at lower cost.

The Free To Choose Medicine (FTCM) option we suggest is a policy proposal that addresses the key constraint to improving the drugs-to-patients system: the lack of consumer choice and competition due to the FDA's monopoly over access to new drugs.[13] Legislation enacting the proposal would establish a dual track system for new drug testing that preserves the existing FDA-controlled process, while offering physicians and patients the choice to use not-yet-approved drugs after preliminary safety and efficacy testing.

The results of this alternative system would be captured in a publicly accessible database, giving patients, doctors, pharmaceutical manufacturers, medical researchers, and regulators up-to-date information about the experience of patients using Free To Choose track drugs. The optional, Free To Choose Medicine route for testing would provide a significantly greater level of choice, promote mechanisms for fast-paced, adaptive learning, and deliver potentially beneficial medicines to patients sooner, and very likely at a lower cost. And the level of actual patient demand for FTCM track drugs would better reflect the true value the public places on earlier access to innovative new drugs.

In Section II, we discuss some of the shortcomings associated with the FDA's standard drug testing and approval model. Section III describes the basic elements of the Free To Choose Medicine reform proposal, while Section IV tackles some of the major criticisms of the idea. Section V concludes.

I. Shortcomings of FDA's Current Process

The FDA, Congress, and public health officials defend the agency's current testing and approval system as providing the gold standard of medical evidence and the best way to ensure the safety and effectiveness of new drugs.[14] Unfortunately, it is also characterized by lengthy and expensive testing methods, long approval times, and flawed decision making.[15] Despite its efforts to approve only drugs whose benefits outweigh their risks, the FDA does sometimes approve drugs that are later found to have serious side effects, and it often fails to approve many useful drugs in a timely manner—leaving millions of patients with inferior treatment options.

The FDA's statutory mission is to ensure that there is "substantial evidence" generated from "adequate and well-controlled investigations" for a new drug's safety and efficacy.[16] But no drug is perfectly safe, in the sense that it has no negative side effects. So, the best outcome we can expect from FDA decision-making is a determination that an approved product's benefits outweigh its risks for the typical patient. That requires a judgment call, however. And, when making such judgments, the agency faces very potent incentives to "err on the side of caution."

If it approves a drug that later is found to be unsafe in any way, the news media, the public, and politicians blame FDA for the error. On the other hand, if the agency delays when reviewing applications, or inappropriately rejects a product that would deliver net benefits, the patients who need innovative new treatments are worse off, and some may even die waiting for FDA to act. In both cases, patients are hurt, but FDA is primarily criticized for approving risky medicines—rarely for keeping beneficial ones off the market.

The agency has been further criticized for its "inability to keep up with scientific advances" in a field that has "undergone revolutionary change" in recent decades.[17] A 2007 report by the FDA Science Board concluded that "FDA's evaluation methods have remained largely unchanged over the last half-century,"[18] and that "[i]nadequately trained scientists are generally risk-averse, and tend to give no decision, a slow decision or even worse, the wrong decision on regulatory approval or disapproval."[19]

As a result, the agency has developed an entrenched, progressively more risk-averse culture, so that it now requires longer clinical trials, stricter post-marketing monitoring, and quicker drug withdrawals. All of these decrease patient options, contribute to rising drug prices, and lead to unnecessary suffering and death. Still, the potent political incentives the agency faces cause it to seek greater and greater certainty from clinical trials that are longer, more intricate, and more costly.

The standard process of new drug testing is a lengthy and expensive one that begins with preclinical laboratory research, which includes extensive in vitro analyses and animal testing. Once a promising drug candidate is selected from the thousands of compounds tested in the laboratory, the FDA must grant permission for the manufacturer to begin a three-step series of human clinical trials:[20]

- In Phase I, a small number of healthy volunteers (generally in the range of 20 to 100) are given the drug in increasingly large doses in order to determine a safe level of exposure.
- In Phase II, a larger number of patients with the actual disease (typically from 100 to 500) are given the drug to further evaluate its safety and to establish an effective dosage level.

- Phase III trials generally involve 1,000 to 5,000 patients, roughly half of whom receive the experimental drug, while the other half receive either a placebo or, where one exists, the current standard treatment for the disease. Patients are randomly assigned to the active test or control group, and knowledge of which get the test drug and which the placebo is concealed from both the patients and their treating physicians to minimize biases and preconceptions held by individual experimenters.[21]

In order to fine tune dosing regimens and begin understanding efficacy and the drug's mechanism of action, developers will often conduct numerous Phase I and II trials for each product. And, in most cases, the FDA requires manufacturers to conduct at least two Phase III trials, in order to provide a high degree of confidence in the drug's safety and efficacy.

Once a manufacturer completes all of this research and concludes it has a marketable drug, it submits a New Drug Application (NDA) to the FDA. The NDA includes all the data from every preclinical and clinical test conducted, and a request that the agency approve the drug in one or more dosage forms for the treatment of a specific medical condition.[22] The entire process, from drug discovery to FDA approval, takes from 10 to 15 years to complete, with clinical trials alone taking an average of six to seven years.[23] And because just one in 12 drugs that enter human clinical trials are eventually approved by the FDA, total accumulated costs for bringing one new drug to market average approximately $1.5 to $1.8 billion dollars.[24]

Since 1992, FDA has also had an "accelerated approval" track for drugs that treat serious conditions for which no other treatments are available. In certain circumstances, such drugs may be granted limited approvals after a single Phase III trial (or on rare occasions, after Phase II trials are complete) under the condition that the manufacturer continue conducting additional Phase III trials to demonstrate safety and efficacy.[25] The agency will also "fast track," or expedite, its reviews of New Drug Applications for products designed to treat serious conditions that have no proven treatment options or where the new drug is substantially more effective than alternatives. Or it may designate drugs intended to treat serious conditions with an unmet medical need as "breakthrough therapies," which may be approved on the basis of a substantial reduction in symptoms or other serious consequences of the disease, rather than evidence that the product cures the disease per se.[26]

At best, these faster reviews get innovative new drugs to market a year or two sooner than would otherwise be the case. To be sure, for critically ill patients, that modestly quicker access is important. But these tweaks clearly do not represent major improvements to the standard approval pathway. Moreover, whether a drug proceeds through the FDA's standard system or one of these accelerated approval processes, most patients—including those who are seriously ill and have no other viable medical options—never have the choice to be treated with an experimental drug that may save their lives. Because clinical trials demand homogeneous cohorts of patients with similar physical characteristics and disease progression, most patients are not even eligible to participate in a trial. And, even if a trial were available and a given patient able to enroll, he or she is often just as likely to receive a placebo as the experimental drug.

The FDA does operate an expanded access, or "compassionate use," program in which patients who are ineligible for clinical trials may sometimes be given permission to use an experimental drug outside the RCT system.[27] However, like the clinical trial process itself, the procedures and requirements for being granted a compassionate use exemption are complex, rigid, and burdensome, and many patients find that they are denied access altogether or that permission is granted too late for the drug to have any effect in terminally ill patients.[28]

On the face of it, this is an egregious injustice that denies millions of patients the opportunity to bear the risks associated with taking experimental medicines that could save or extend their lives. Yet this is what current law demands in order to meet the statistical requirements of the FDA's clinical trial methodology, which, despite its scientific merits, nevertheless provides only an imperfect look at a drug's true safety and efficacy profile under real world conditions.

First developed over half a century ago, randomized placebo controlled trials are good for detecting when medical interventions have large effects on populations of similar patients. Yet, the homogeneous patient pools and tightly controlled clinical environments associated with randomized drug trials do not reflect real-world practice and outcomes very well. Once drugs are approved and prescribed to tens of thousands, or millions, of patients at different stages of disease and with vastly differing health characteristics, co-morbidities, and lifestyles, the seemingly robust results of a clinical trial often fail to stand up over time.[29]

Randomized controlled trials (RCTs) are also ill suited for detecting and testing subtle differences that occur in small patient subpopulations, which makes them poor tools for fast-paced, adaptive learning. To minimize the occurrence of hindsight bias in data analysis, clinical trials begin with a hypothesis and a carefully constructed methodology for testing that hypothesis.[30] When an unexpected or idiosyncratic effect is detected among a subpopulation of the test group, the FDA typically demands that the manufacturer form a new hypothesis and initiate an entirely new trial. In the process, adaptive learning is short-circuited, and the cost of drug development rises still further.

In March 2007, an FDA advisory committee comprised of independent scientific and medical experts voted 17 to zero that an innovative prostate cancer drug called Provenge was safe enough for approval, and it voted 13 to 4 that Provenge demonstrated substantial evidence of efficacy. Advisory committee recommendations are very often followed by the agency, so many observers assumed that such a robust recommendation would lead to a quick FDA approval. But two months later, the agency denied approval because the drug failed to meet its trial's primary target endpoint.[31] Instead, the agency suggested the manufacturer should initiate another Phase III trial, and did not approve Provenge until two years later.[32]

Still, while the FDA insists we can have no confidence in the value of new medicines until their efficacy has been validated in Phase III clinical trials, millions of patients each year

are treated successfully with medicines whose effectiveness was never studied in a clinical trial. When the FDA approves new drugs, they are certified as safe and effective for the particular use tested in the underlying clinical trials, and that indication is placed on the FDA-approved label. However, once a drug is approved by the agency, physicians may legally prescribe it "off-label" to treat other diseases or medical conditions.[33] For example, an oncology drug called Platinol has been approved for the treatment of bladder, testicular, and ovarian cancer. But, because its mechanism of action is well known to physicians, Platinol is now frequently and fruitfully prescribed to treat different kinds of cancerous tumors, including thyroid and lung cancers, even though its effectiveness for those indications has not been validated in RCTs.[34]

Many off-label uses are discovered by drug and device manufacturers or academic researchers who conduct clinical trials with the hope of generating data to support an FDA approval for new label indications. But practicing physicians often discover new and important off-label uses on their own—by, for example, observing the beneficial side effects of certain medicines or by applying their knowledge of chemistry and physiology to use remedies approved for one illness to treat other illnesses with similar underlying causes. One study found that 59 percent of drug therapy innovations were discovered by practicing physicians in the field, independent of pharmaceutical company or university research.[35]

The practice of off-label prescribing is widespread, and is common in every field of medicine. By some estimates, at least 20 percent of all prescriptions written are for off-label uses,[36] and most hospital patients receive at least one drug off-label.[37] Indeed, off-label uses are frequently considered to be state of the art treatment, and often constitute the medically recognized standard of care.[38] Consequently, physicians may even be subject to malpractice liability if they do not use drugs for off-label indications when doing so constitutes the medically recognized standard of care.[39] The successful and widespread use of off-label prescribing is testament to the ability of valuable medical knowledge to arise from information learned outside the RCT process.

II. Free To Choose Medicine

Despite its shortcomings, the standard FDA process nevertheless has its defenders. So, under the Free To Choose Medicine proposal, this standard FDA testing and review track would remain in place and unchanged. Patients and doctors who trust only the rigid FDA approval system would be free to rely on only FDA approved medicines.

However, after making a preliminary demonstration of safety and efficacy by completing Phase I trials and at least one Phase II trial, drug manufacturers would be given the option to place an experimental product on a parallel Free To Choose track that would enable patients, advised by their doctors, to make an informed choice to use the experimental drug. Drug makers could opt to continue pursuing a standard FDA approval—with all the attendant clinical testing that would require—concurrent with placing a drug on the Free To Choose track. Or, they could put off standard FDA-regulated clinical trials indefinitely, using Free To Choose track experience to guide future development decisions and randomized control trial designs.

As illustrated in Figure 1, the conventional track consisting of Phase I, II, and III clinical trials and FDA review would be maintained for manufacturers seeking standard FDA approval. On a separate track, operated independently of the FDA, patients, advised by their doctors, could make informed decisions either to use an approved drug or to contract with a drug developer to buy a promising, not-yet-FDA-approved drug that has demonstrated success in at least one Phase II safety trial. Although substantially greater choice would be afforded to patients, the Free To Choose track would still proceed under the aegis of a federally regulated body and be designed to capture information about safety and effectiveness from individual patients.

The heart of this dual track system would be an information aggregation and sharing tool called the Tradeoff Evaluation Drug Database (TEDD). Upon placing a drug on the Free To

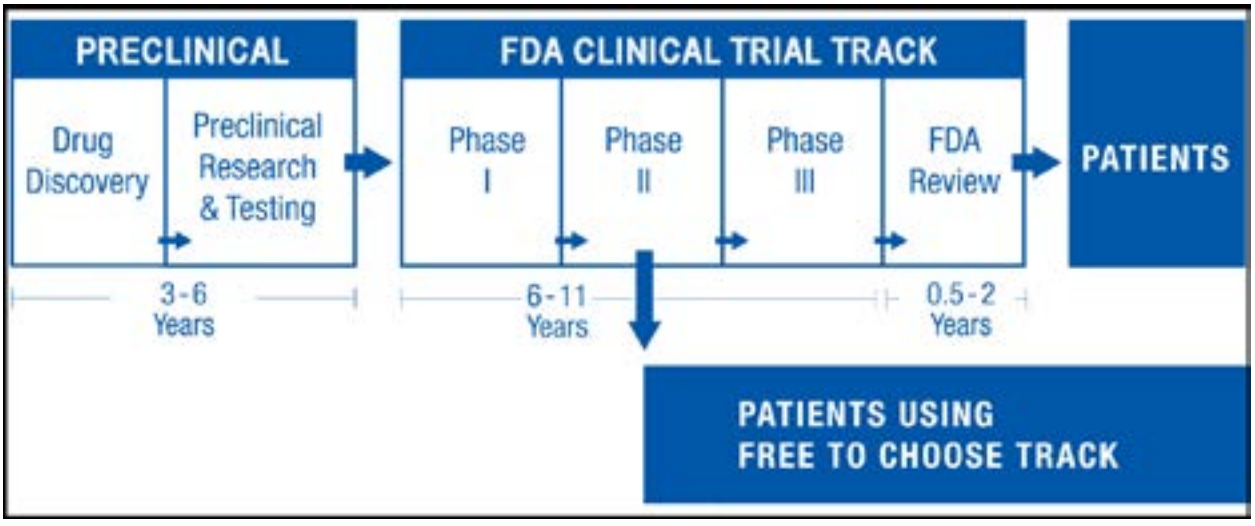

Figure 1. The Dual Track System Enables Choice

Choose track, drug makers would be required to make available a complete dossier of preclinical and clinical testing data, along with any other evidence it has relating to the product's safety and its effectiveness or ineffectiveness in human patients. The TEDD would also contain additional information regarding the recommended dosage and duration of use, known interactions with other drugs, and other counterindications. And manufacturers would be obligated to update this initial submission with all additional such information arising from on-going clinical trials or reported by physicians, patients, regulatory and public health authorities, independent researchers, or others. Information in the database would be made available to the public through a government-supervised web portal, and it would provide patients and doctors with the information they need to make informed decisions about a drug's potential benefits and risks before choosing to use it.

The TEDD would also permit physicians and patients to engage in dynamic analysis and play a role in the learning experience. Before a doctor could prescribe a Free To Choose track drug, the patient would need to certify that he or she has been informed of the product's experimental nature and also agree to permit the physician to upload de-identified information about the patient's age, sex, physical characteristics, health status, and relevant genetic biomarkers—that is, stripped of any information that could identify the individual patient. Physicians would also be required to submit periodic updates on the patient's treatment progress, adverse effects, and health outcomes.

This up-to-date observational data on treatment outcomes would ensure that patients and doctors know, in real time, what drug developers know about every drug available on the Free To Choose track. It would also be an invaluable resource for drug makers themselves, providing information that can be used in designing conventional, randomized controlled clinical trials and providing insights to improve ongoing research and development activities. In addition to monitoring whether a drug causes any unexpected, adverse side effects among users, these observational studies would yield greater insights on minimum and maximum dosage and effectiveness in a heterogeneous patient population that mimics real world use better than tightly controlled clinical trials do.

In sharp contrast with rigidly designed clinical trials, discovery that a Free To Choose track drug is especially effective or problematic for small patient subpopulations could immediately result in voluntary, increased or decreased use by others who have health profiles that match the particular subpopulation. Hence, more and more observational data would be accumulated that sheds a powerful light on the validity of initial findings. And this could occur rapidly, without the enormous delay inherent in conducting additional Phase III trials focused on the identified subpopulations.

For those drugs that developers elect to put on the Free To Choose track, patients could gain quicker access by up to eight years compared to waiting for the completion of Phase II and III testing and standard FDA approval. And the Tradeoff Evaluation Drug Database would help patients and their physicians evaluate the benefit/risk profile of a promising new drug with relevant, up-to-date information, as shown in Figure 2.

Importantly, information in the TEDD regarding Free To Choose track drug use would provide real-time, observational data showing the safety and effectiveness, or lack thereof, for new drugs. Inclusion of a wealth of relevant data on patient characteristics would also help physicians and manufacturers identify sub-populations of patients that do especially well or poorly. And, for promising new drugs that address serious illnesses, as more and more patients learned of early treatment successes and opted to try these drugs themselves, the TEDD could soon contain significantly more patient outcome reports

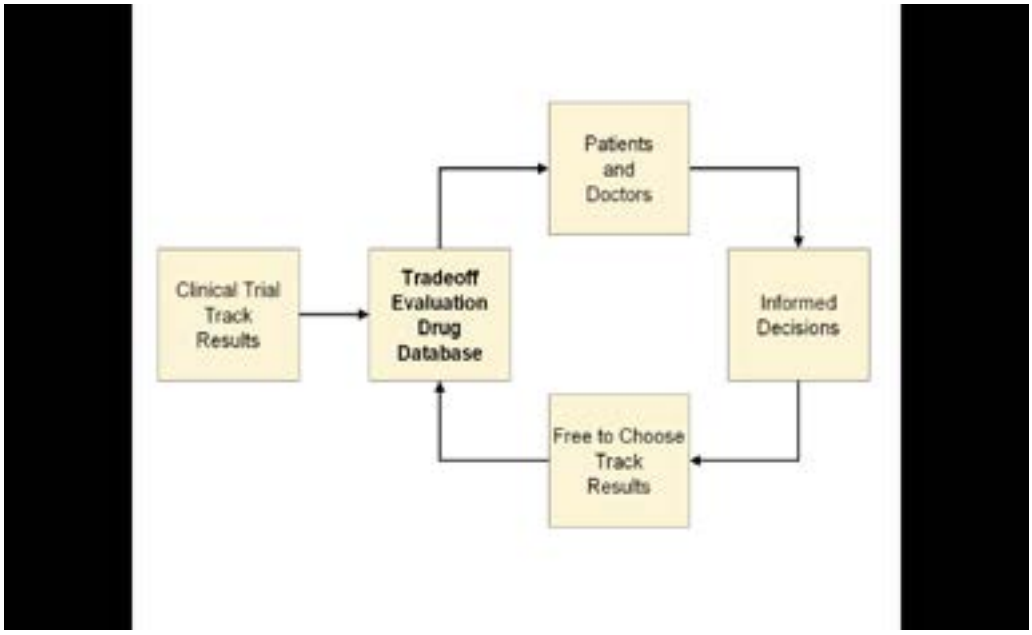

Figure 1. The Dual Track System Enables Choice

than are available from standard clinical trials. In turn, certain Free To Choose track drugs may well become the medically recommended standard of care for individual illnesses, just as many off-label uses have. And in time, pending enactment of an "Observational Approval" pathway, Free To Choose track experience could also form the basis for an FDA marketing approval based in whole or in part on observational data in the TEDD.

In order to prevent the objectives of the Free To Choose Medicine proposal from being undermined by an overly protective FDA, the TEDD and other Free To Choose track functions would have to be operated by a separate but still competent authority, such as the National Institutes of Health. Furthermore, not every drug completing Phase II trials would be automatically eligible for Free To Choose track status. A Free To Choose Medicine Advisory Committee, comprised of physicians, patient advocates, and medical experts, would be established within the NIH to determine which experimental drugs are sufficiently promising to merit entry on the FTCM track and to monitor the TEDD to determine when drugs should be removed because risks clearly outweigh their benefits.

Naturally, because manufacturers and patients would be the beneficiaries of the dual track system, it would be incumbent upon them to pay the majority of its costs. Upon submission of a request to enter a drug on the FTCM track, a manufacturer would have to certify its willingness to offset all the NIH's costs associated with maintaining the Tradeoff Evaluation Drug Database records for that drug. Similarly, because private health plans with pharmaceutical coverage generally do not pay for experimental treatments, most patients electing to use a FTCM track drug would have to pay the price out of pocket.

That payment constraint, combined with the fact that FTCM track drugs are experimental, should incentivize drug makers to set lower prices than they could demand for fully FDA approved products. In time, though, as individual Free To Choose track drugs amassed a record of success in treating certain diseases, prices for those products could be expected to rise. At the same time, it is possible that some insurers would be willing to add products to their standard formularies or create a special reimbursement policy for FTCM drugs whose benefits outweighed their risks and that performed better than alternative treatment options, just as they do now for certain off-label uses. Congress might, however, also be encouraged to create a small demonstration project within Medicare and Medicaid to determine whether certain FTCM track drugs could be reimbursed while reducing payments for treatment alternatives.

Finally, because FTCM drugs will be experimental, doctors would need to be granted limited immunity from malpractice claims, and manufacturers would need to be granted limited immunity from lawsuits claiming design defect or negligent failure to warn against adverse side effects. Under tort law standards, FDA approved medicines are viewed as unavoidably unsafe and generally are not deemed defective so long as they are "properly prepared and marketed, and proper warning is given."[40] Negligent failure to warn claims, however, are endemic in the pharmaceutical industry, and juries often find manufacturers liable even when copious warnings are supplied in the product's labeling.[41] And a design defect claim may be sustained "if the foreseeable risks of harm … are sufficiently great in relation to [the product's] foreseeable therapeutic benefits that reasonable health care providers … would not prescribe the drug or medical device for any class of patients."[42]

By their very nature, the benefits and risks of experimental drugs will be poorly characterized when first entered on the FTCM track. Consequently, "proper warning" of their attendant risks may be impossible to provide until their use is extensive enough to draw firm conclusions about their safety and effectiveness. Skeptics may even argue that any use by a physician should be considered negligent, however well informed and willing the patient may have been to bear the risk. And the novelty of the Free To Choose Medicine approach makes it unclear whether liability waivers, such as those signed by patients enrolled in clinical trials, would be upheld in court, or whether courts might create an exception to the unavoidably unsafe defense. Therefore, legislation implementing the FTCM process should grant physicians immunity from malpractice claims and grant manufacturers immunity for design defect or negligent failure to warn claims, except in the case of gross negligence or willful misconduct, so long as patients certify they have been informed of the product's experimental nature.

IV. Addressing the Criticisms

The most common justification for FDA's monopoly control over access to new drugs is that patients and doctors are not equipped to make decisions about not-yet-approved drugs. In nearly all cases, drug makers have the most comprehensive information about the benefits and risks of their products,[43] but busy clinicians lack the time and expertise to make a comprehensive analysis of the full body of data, even if it were available to them. For their part, the typical patient is certainly not in a position to comprehend this complex information and make reasoned risk/benefit balancing choices, the thinking goes.

The Free To Choose Medicine approach is designed specifically to address these concerns. Manufacturers would be legally obligated to make public all data relevant to safety and efficacy, and it would be displayed on the TEDD in an easily accessible format. We could expect medical professional societies, patient advocacy organizations, and other medical researchers to scour the available evidence and make recommendations on how and whether to use FTCM track drugs, just as they do with off-label drug uses.[44] And physicians would be there to guide their patients every step of the way.

The assumption that a body of governmental experts is necessary to weigh a drug's risks and benefits is fatally flawed. Ignored is the fact that individuals have different preferences for risk, and that many would be willing to choose a product they know to pose a substantial risk of harm in order to gain the opportunity to treat or cure a life threatening or seriously debilitating disease. Individual preferences are not—and, by and large, cannot be—recognized in the current one-size-fits-all regulatory process. Under the current regime, risk averse patients have the option of not taking an FDA-approved medicine until they and their physicians are convinced by broad use in a non-experimental population that the product

is safe and effective. But those who would tolerate the added risk of a drug whose risk/benefit profile is not fully known are denied that choice.

As for the claim that patients lack the ability to assess the value of experimental drugs, the Abigail Alliance, a patient advocacy organization that helps people gain compassionate use exemptions to access not-yet-FDA-approved medicines, has shown that argument to be flawed. In its brief history, the Abigail Alliance has targeted 21 experimental cancer drugs that, in its judgment, offered great enough benefits and low enough risks to justify their use. All 21 drugs were subsequently approved by the FDA, but too late for many patients who died waiting for that stamp of approval.[45]

Joshua Boger, founder of Vertex Pharmaceuticals, adds:

> In my experience, drugs that do not work and drugs that substantially exceed minimal expectations are easy to spot. While there are exceptions, if you need a statistician to measure benefit in Phase II, then the drug didn't work that well. In a world of profound opportunity to change medicine, maybe we shouldn't be working on those middling cases. Identify as fast as possible the drugs that don't work (and learn from them), and identify as fast as possible the upside surprises.[46]

Supporters of the status quo would counter that Phase II testing successes are often illusory and that there is a reason why randomized controlled trials are considered the gold standard for scientific evidence. There is no doubt that the FDA's current approach helps medical experts draw the most statistically valid conclusions. It is also slow, cumbersome, and expensive. It also denies millions of patients the choice to control one of "the most intimate and personal choices a person may make."[47] Indeed, the exponential growth in recent years of websites designed to help patients share information about treatment options is a strong indication that many patients would embrace an opportunity to take a greater role in their medical decision-making.

One of the many websites that harnesses collective intelligence on medical treatments is www.PatientsLikeMe.com. It began as a social network for people with amyotrophic lateral sclerosis (better known as ALS or Lou Gherig's disease) and has since expanded to cover a number of other serious illnesses. Participants share personal information about the progression of their diseases, treatment options including their use of various medicines, side effects, and other successes and setbacks. The success of this and similar websites confirm that people are willing, and in some cases eager, to share information that can not only help their own decision-making but also help others.[48]

PatientsLikeMe has also shown that valuable scientific research can be generated from observational studies of pharmaceutical use by real world populations. In one initiative, the organizers of PatientsLikeMe conducted a study of lithium use by ALS patients participating in the site. Doctors often prescribe lithium to ease the debilitating symptoms associated with ALS, even though there is considerable uncertainty about its effectiveness. So, researchers at PatientsLikeMe analyzed observational data for participants' lithium use and discovered that it had no effect on disease progression—an important finding that is likely to have broad impacts on the treatment of ALS patients. The organizers subsequently published their results in the prestigious journal *Nature Biotechnology*, concluding that:

> Although observational studies using unblinded data are not a substitute for doubleblind randomized control trials, this study reached the same conclusion as subsequent randomized trials, suggesting that data reported by patients over the internet may be useful for accelerating clinical discovery and evaluating the effectiveness of drugs already in use.[49]

Free To Choose Medicine would represent a paradigm shift away from glacially slow, bureaucratic machinery to a fast-paced, learning system attuned to exploiting technological advancements in large-scale data analysis and in biochemical science. These advancements suggest less reliance is needed on RCTs to answer the question of whether a drug works, on average, for a homogeneous sample of patients in a clinical trial. In recent years, our ability to collect, store, aggregate, and analyze the relationship among millions of individual data points has risen by many orders of magnitude, while costs have plummeted.[50]

Today, the same sophisticated computational power that makes electronic commerce and targeted marketing possible can be, and is being, marshaled for use in a broad range of medical research applications.[51] Indeed, health researchers are eagerly awaiting the increased use of electronic medical records mandated by the Patient Protection and Affordable Care Act for the very reason that it will enhance their ability to analyze the safety and efficacy of various medical interventions in real-world application and to tease out very narrow sub-population by sub-population results.[52] Technology entrepreneur Andrew Grove believes that using this kind of analytical tool to evaluate experimental medicines:

> would liberate drugs from the tyranny of the averages that characterize trial information today. The technology would facilitate such comparisons at incredible speeds and could quickly highlight negative results. As the patient population in the database grows and time passes, analysis of the data would also provide the information needed to conduct postmarketing studies and comparative effectiveness research.[53]

While we appreciate the power of RCTs as a scientific tool, the systems mindset reminds us that learning is a complex process occurring in both controlled and uncontrolled environments. Most of the information on which we base important decisions about our lives is learned from sources that fall well short of a "gold standard." In fact, aside from the introduction of new drugs and medical devices, much of the current practice of medicine was adopted without benefit of randomized trials. Most studies of surgical procedures are based solely on retrospective analysis of practices adopted by trial and error innovation.[54] And, as discussed above, the majority of off-label drug uses are discovered by practicing physicians in the field without prior validation in randomized trials.[55] Thus, observational data is already delivering tremendous value in the treatment of real

world patients.

Indeed, some critics of giving patients expanded access to not-yet-FDA-approved drugs may be concerned that demand for Free To Choose Medicine opportunities would be quite high. One of the biggest challenges associated with enrolling test subject in clinical trials is the knowledge that as many as half of enrollees will not have access to the experimental drug, but will be given a placebo or an alternate treatment. Making it possible for patients who wish to use such products to bypass the clinical trial regime would, in their view, "threaten[] to undermine the willingness of patients and manufacturers alike to participate in clinical trials."[56] Their solution is to give patients and manufacturers no other option but to support the RCTs necessary for standard FDA approval.

The assumption made by the FDA and its defenders appears to be that, while it may be unfortunate that today's patients are denied access to the newest medicines, "carefully controlled trials … are the fastest, most efficient way to determine what treatments work. … Conducting well-designed trials from the beginning will benefit more patients, sooner, than any other approach."[57] But that assumption follows from their view that it is acceptable to sacrifice individual patients for the good of society overall, a view we do not share. It also runs counter to the growing body of evidence that the rising cost and burden of clinical trials is causing manufacturers to abandon promising medical treatments long before New Drug Applications are filed, which includes shutting down clinical and pre-clinical development projects they believe would yield an inadequate return on investment given the status quo regulatory environment.[58]

Finally, the rigid defense of RCTs as the only reasonable way to evaluate new drugs suggests that defenders of the status quo are unwilling to consider the very valuable role that observational studies of real world patient populations play. In at least in some cases, though, observational studies have proven superior to slow, expensive, and cumbersome randomized controlled trials. In our view, many patients may be reluctant to take advantage of FTCM track medicines for the sole reason that they remain experimental, but the choice to do so or not would belong to them. The argument that patients must become sacrificial lambs in order to facilitate the FDA's statistical analyses using RCTs is unacceptable.

Conclusion

The more one looks at how uncertainty is handled in the real world, the more suspect becomes the FDA's presumption that the world of new drugs is too complex for patients to handle effectively. Patients and their doctors are already grappling with the uncertainties of illness, with the weighing of risks and benefits of varying treatment options, and myriad other complex decisions. Neither Congress nor the FDA knows what the optimal level of testing is, nor how much risk is appropriate for every patient. But in its zeal to generate the strongest possible evidence of safety and efficacy, the FDA has preserved a system that raises costs, prolongs development times, and restricts the number of new medicines brought to market. What is needed is an alternative that would be consistent with the goal of better drugs, sooner, at lower cost.

The solution is a dynamic, market-based dual track system that self-adjusts in response to the effectiveness of new drugs. An environment of more and more patients benefitting from early access would become strong feedback to the FDA that its regulatory demands are excessive. Free To Choose Medicine would bring competition for the FDA that would compel real innovation in the FDA's standard approval process. Arguably more important is the empowerment of patients who are fighting life-threatening illnesses to gain early access to the most innovative new drugs that could substantially improve their quality of life or save their lives.

For drug developers, the economic cost of delayed revenue generation would be greatly reduced if they could sell their drugs on the Free To Choose track. Currently, both venture capitalists and drug developers face a disincentive in backing a radical new drug development program that invariably faces unknown Phase III testing demands. Imagine what a different investment environment there would be if up to eight years could be cut from the commercialization timeline and success is solely determined by how well the new drug works in actual use, instead of having to deal with Phase III statistical milestones that, for a drug based on a radically new approach, might be unreasonably difficult to achieve.

In a competitive environment, when companies' costs drop, consumers benefit from lower prices. Moreover, competition in the pharmaceutical industry would intensify as Free To Choose Medicine put a premium on demonstrated scientific skill in developing breakthrough drugs to a far greater degree than skill in navigating the FDA's bureaucracy. In addition, the costs of Phase II and especially Phase III testing would drop over time as the FDA was compelled to streamline its testing demands more rapidly because the opportunity cost of delayed access would now become visible. The end result would be a path forward that would dramatically lower the cost of therapeutic drugs and deliver more of them to the marketplace.

No one would be forced to use unapproved drugs. In fact, patients with an extreme concern for safety would actually benefit from their use of only FDA-approved drugs if heavy use of those products on the Free To Choose track generated more robust information about their effects in real world patient populations. It is much more likely that safety issues and side effects would be identified from a large, pool of heterogeneous, Free To Choose patients than a small population of homogeneous patients in clinical trials.

We already see the benefits of today's doctor and patient-driven initiatives in better medical treatment outcomes, ranging from off-label use to the popularity of websites such as PatientsLikeMe, which facilitate the sharing of treatment innovation and improving knowledge of what works. Implementing Free To Choose Medicine would create a new information-based American industry that facilitates data transmission from doctors to the TEDD as well as the analysis and distribution of high value, TEDD-derived information.

No longer should we be complacent and accept the plight of existing patients who are denied the choice that might materially improve or save their lives. It is a tragic mistake to accept the FDA's assumption that the enormous time and money costs

of Phase II and III clinical trials are a necessary cost to be paid in order to benefit future patients.

Endnotes

1 Ben Hirschler & Caroline Humer, *FDA new drug approvals hit 16-year high in 2012*, Reuters, Dec. 31, 2012, *available at* http://www.reuters.com/article/2012/12/31/us-pharmaceuticals-fda-approvals-idUSBRE8BU0EK20121231.

2 *See*, *e.g.*, Food and Drug Administration, FY 2012 Innovative Drug Approvals: Bringing Life-saving Drugs to Patients Quickly and Efficiently (Dec. 2012), *available at* http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm330859.pdf; Samantha A. Roberts, Jeff D. Allen & Ellen V. Sigal, *Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe*, 30 Health Affairs 1375 (2011).

3 Rita Rubin, *How did Vioxx debacle happen?* USA Today, Oct. 12, 2004, at 1D.

4 Steven Reinberg, *FDA to Pull Diabetes Drug Avandia From Pharmacy Shelves*, U.S. News & World Report, May 19, 2011, *available at* http://health.usnews.com/health-news/diet-fitness/diabetes/articles/2011/05/19/fda-to-pull-diabetes-drug-avandia-from-pharmacy-shelves.

5 David L. Gollaher, Simon Goodall & Christi Whittemore, California Healthcare Institute & Boston Consulting Group, Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry (2011), *available at* http://www.chi.org/uploadedFiles/Industry_at_a_glance/Competitiveness_and_Regulation_The_Future_of_America%27s_Biomedical_Industry.pdf.

6 Tufts Center for the Study of Drug Development, *Growing Protocol Design Complexity Stresses Investigators, Volunteers*, 10 Tufts CSDD Impact Report, no.1 (2008), *available at* http://csdd.tufts.edu/files/uploads/jan-feb_impact_report_summary.pdf.

7 Tufts Center for the Study of Drug Development, *Rising protocol complexity, execution burden varies widely by phase and TA*, 12 Tufts CSDD Impact Report, no. 3 (2010), *available at* http://csdd.tufts.edu/files/uploads/mayjuneimpactrpt10summary.pdf.

8 Tufts Center for the Study of Drug Development, *89% of trials meet enrollment, but timelines slip, half of sites under-enroll*, 15 Tufts CSDD Impact Report, no. 1 (2013), *available at* http://csdd.tufts.edu/files/uploads/janfeb_2013_ir_summary.pdf.

9 Malorye Allison, *Reinventing clinical trials*, 30 Nature Biotechnology 41-49 (2012).

10 *Id.*

11 *See* Food and Drug Administration, Public Hearing; Request for Comments: Modernizing the Regulation of Clinical Trials and Approaches to Good Clinical Practice, 77 Fed. Reg. 13,513 (Mar. 7, 2012).

12 Bartley J. Madden, Wealth Creation: A Systems Mindset for Building and Investing in Businesses for the Long Term (2010).

13 For a broader discussion, see Bartley J. Madden, Free To Choose Medicine: Better Drugs Sooner at Lower Cost (2d ed., LearningWhatWorks, Inc. 2012).

14 *See, e.g.*, Food and Drug Administration, *Guidance For Industry: Providing Clinical Evidence Of Effectiveness For Human Drugs And Biological Products; Availability*, 63 Fed. Reg. 27093 (May 15, 1998); Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 Food & Drug L.J. 299 (2003); Brief for National Association of Rare Disorders et al. as Amici Curiae Supporting Appellees, *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (No. 04-5350).

15 *See, e.g.*, FDA Science Board, FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology (2007); Henry I. Miller, To America's Health: A Proposal to Reform the Food and Drug Administration (2000).

16 21 U.S.C. § 355 (2012).

17 FDA Science Board, *supra* note 15, at 3.

18 *Id.*

19 *Id.* at 5.

20 For a broader discussion, see Geoffrey M. Levitt, *The Drugs/Biologics Approval Process*, *in* A Practical Guide to Food and Drug Law Regulation 113 (Kenneth R. Pina & Wayne L. Pines eds., 2008).

21 *See* Ronald. A. Fisher, The Design of Experiments (1st ed. 1935).

22 Levitt, *supra* note 20.

23 Pharmaceutical Research and Manufacturers of America, 2013 Biopharmaceutical Research Industry Profile (2013).

24 *See* J. Mestre-Ferrandiz, J. Sussex & A. Towse, Office of Health Economics, The R&D Cost of a New Medicine (2012); S.M. Paul et al., *How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge*, 9 Nature Reviews Drug Discovery 203-14 (2010).

25 Food and Drug Administration, *Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review Expediting Availability of New Drugs for Patients with Serious Conditions*, http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm (last visited Aug. 15, 2013).

26 *Id.*

27 Expanded Access to Investigational Drugs for Treatment Use, 21 C.F.R. § 312 subpart I (2013).

28 *See, e.g.*, Jerome Groopman, *The Right to a Trial: Should dying patients have access to experimental drugs?* The New Yorker, Dec. 18, 2006, at 40; Editorial, *How About a 'Kianna's Law*'? Wall St. J., Mar. 24, 2005, at A22; Gregory Conko, Op-Ed., *Sick Patients Need Cutting-Edge Drugs*, Wall St. J., Aug. 23, 2008, at A11.

29 *See* David M Kent & Georgios Kitsios, *Against pragmatism: on efficacy, effectiveness and the real world*, 10 Trials 48 (2009); Susan D. Horn, *Real-World Efficacy*, 10 Drug Discovery & Development 30 (2007); Michael H. Davidson, *Differences Between Clinical Trial Efficacy and Real-world Effectiveness*, 12 Am. J. Managed Care. S405 (2011).

30 *See* Fisher, *supra* note 21.

31 Editorial, *The regulator disapproves*, 26 Nature Biotechnology 1 (2008).

32 *FDA Approves a Cellular Immunotherapy for Men with Advanced Prostate Cancer*, FDA News Release, Apr. 29, 2010, *at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm210174.htm.

33 *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001); David A. Kessler, *The Regulation of Investigational Drugs*, 420 New Eng. J. Med. 281, 288 (1989).

34 National Cancer Institute, *Understanding the Approval Process for New Cancer Treatments, Q&A: Off-Label Drugs*, *at* www.cancer.gov/clinicaltrials/learning/approval-process-for-cancer-drugs/page5 (last visited Aug. 15, 2013).

35 Harold J. DeMonaco, Ayfer Ali & Eric A. Von Hippell, *The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies* (MIT Sloan Research Paper No. 4552-05, 2005), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=780544.

36 David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-label Prescribing Among Office-Based Physicians*, 166 Archives Internal Med. 1021-26 (2006).

37 James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L.J. 71 (1998).

38 American Medical Association House of Delegates, "Patient Access to Treatments Prescribed by Their Physicians," AMA House of Delegates Health and Ethics Policy H-120.988; Reaffirmed by AMA House of Delegates Resolution 918 (October 2007), http://www.ama-assn.org/ama1/pub/upload/mm/469/i07918.doc.

39 Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 Fla. L. Rev. 181,

190-91 (1999).

40 Restatement (Second) of Torts §402A cmt. k (1965).

41 *See*, *e.g.*, Wyeth v. Levine, 555 U.S. 555 (2009) (drug label warned multiple times of the specific injury suffered by plaintiff, but jury concluded a more forceful warning may have prevented the injury; court held recovery was not preempted by FDA approval).

42 Restatement (Third) of Torts: Products Liability §6(c) (1998).

43 *See* Food and Drug Administration., *Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices*, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994) ("Scientific departments within regulated companies generally maintain a large body of information on their products"); *Wyeth*, 555 U.S. at 578-79 (2009) (noting that manufacturers "have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge.").

44 Gregory Conko, *Hidden Truth: The Perils and Protection of Off-Label Drug and Medical Device Promotion*, 21 Health Matrix: J. L. Med. 149 (2011).

45 Abigail Alliance for Better Access to Developmental Drugs, http:www.abigail-alliance.org (last visited Aug. 15, 2013).

46 Joshua Boger, *To boost R&D, stop flying blind and start observing*, *Beyond Borders: Global biotechnology report 2012,* Ernst & Young, 2012.

47 Abigail Alliance For Better Access to Developmental Drugs v. von Eschenbach, 445 F.3d 470, 480 (D.C. Cir. 2006) *rev'd on reh'g en banc*. 495 F.3d 695 (D.C. Cir. 2007).

48 Amy Dockser Marcus, *ALS Study Shows Social Media's Value as Research Tool*, Wall. St. J., Apr. 25, 2011, at A5.

49 Paul Wicks, Timothy E. Vaughan, Michael P. Massagli & James Heywood, *Accelerated Clinical Discovery Using Self-Reported Patient Data Collected Online and a Patient-Matching Algorithm*, 29 Nature Biotechnology 411 (2011).

50 Andrew Grove, *Time to Rethink Clinical Trials*, 333 Science 1679 (2011).

51 *See*, *e.g.*, Food and Drug Administration, Availability of Masked and De-identified Non-Summary Safety and Efficacy Data; Request for Comments, 78 Fed. Reg. 33,421 (June 4, 2013).

52 Paul Cerrato, *Health IT's Next Big Challenge: Comparative Effectiveness Research*, Information Week, Aug. 21, 2012, http://www.informationweek.com/healthcare/clinical-systems/health-its-next-big-challenge-comparativ/240005790.

53 Grove, *supra* note 50.

54 Peter McCulloch, Irving Taylor, Mitsuru Sasako, Bryony Lovett & Damian Griffin, *Randomised trials in surgery: problems and possible solutions*, 324 Brit. Med. J. 1448 (2002).

55 DeMonaco et al., *supra* note 35.

56 *See* Brief for National Association of Rare Disorders et al. as Amici Curiae Supporting Appellees, Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695 (D.C. Cir. 2007) (No. 04-5350).

57 Institute of Medicine, Confronting AIDS 139 (1988).

58 Gollaher et al., *supra* note 5; John Freund, *The FDA Isn't as Innovative as It Likes to Think It Is,* Wall St. J., Aug. 10, 2011, at A14.