LEVIATHAN'S DRUG PROBLEM:

Increasing Patients' Choices through International Competition in Pharmaceutical Regulation

Second Edition, 2010 Report

BY JOHN R. GRAHAM

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Pacific Research Institute
One Embarcadero Center, Suite 350
San Francisco, CA 94111
Tel: 415-989-0833/ 800-276-7600
Fax: 415-989-2411
Email: info@pacificresearch.org
www.pacificresearch.org

Download copies of this study at www.pacificresearch.org.

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FOREWORD

Leviathan's Drug Problem: Increasing Patients' Choices through International Competition brings important evidence to a critical question: How much power should the federal government have over patients' right to choose medicines which might save their lives?

Although John R. Graham's report goes beyond the goals for change at the FDA put forth by the Abigail Alliance, it clearly discusses issues and information that are very relevant to the Abigail Alliance's nine-year effort to save and extend the lives of tens of thousands of cancer patients and others with serious life-threatening illnesses every year. These patients have run out of FDA-approved options, and like so many, cannot get into clinical trials.

Graham's research emphasizes the tragic loss of life due to the slow approval process at the FDA. Reliable sources note that the FDA suffers "organizational dysfunction". Patients with cancer or other serious life-threatening illnesses face a very different risk-benefit profile than those with non-life-threatening illnesses. Tragically, the overly paternalistic FDA is not giving these people a chance to fight for their lives. A decision to take promising investigational therapies should be between the patient and her doctor. Polls reveal what doctors (and the public) want: more tools to fight diseases sooner.

Some of Graham's and others call for change is manifested in Congress' need to pass the Compassionate Access Act (H.R.4732), to allow patients with life-threatening illnesses to use promising new medicines that are still under investigation. The Compassionate Access Act would help American patients, who cannot get into FDA mandated clinical trials, gain access to new medicines to try and save or extend their lives once it is approved by the European Medicines Agency (EMA).

This would have benefited Alita Randazzo, who was diagnosed with colorectal cancer in 2000. Alita had to travel to France to get the drug Eloxatin, which was not approved by the FDA for another three years. Graham's analysis shows that many other patients would benefit from the U.S. government's recognizing European approval of new drugs.

Frank Burroughs
President, Abigail Alliance for Better Access to Developmental Drugs

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EXECUTIVE SUMMARY

When a pharmaceutical innovator invents a new drug, ready for distribution in the United States, the federal government responds by enforcing an automatic ban on patients' use of the drug. Individual patients can escape this ban only under extraordinary circumstances. The general ban is lifted only after the manufacturer has paid a user fee and waited for the Food and Drug Administration (FDA) to undertake a lengthy review to certify the safety and efficacy of the medicine. In 2008, the average time to remove the standard ban on a new prescription medicine was just under 18 months, almost half again longer than it was in 2007.

This lengthening ban is implicated in the deaths of about 200,000 Americans annually, the mid-point of a wide range. Evidence going back more than three decades supports the conclusion that the lost positive outcomes—the ones that would have occurred had the government allowed patients and health professionals to use new drugs faster-~~ov~~erwhelms many times over any decrease in negative health outcomes resulting from avoiding the harmful side effects of new medicines.

Many believe that this failure is due to a lack of money for the FDA, but this is not the case. The number of personnel conducting drug reviews doubled, from 1,300 to 2,600, between 1992 and 2007. More recently, the FDA went on a "hiring surge," taking on 2,500 more employees in 2008 and 2009. Indeed, the agency *exceeded* its hiring targets last year. In FY 2011, the FDA's spending on regulating human drugs will have increased by 20 percent over two years, according to the agency's budget.

During a 12-month period in 2008 and 2009, the European Union's European Medicines Authority (EMA) and the FDA approved a total of 39 new medicines. Fifteen were approved only by the FDA, 11 were approved only by the EMA, and 13 were approved by both regulators. In five of the 13 cases where the FDA and EMA both approved the medicine, the EMA was the first to approve, and it issued those approvals 552 days faster than the FDA, on average. Even if we include all 13 medicines approved by both the FDA and the EMA, the EMA approved them 97 days faster, on average.

If the U.S. government had allowed American patients to use new medicines that were approved by the EMA, but not yet by the FDA, American patients would have had faster access to 17 new medicines, out of the entire set of 39. Clearly, Congress's grant of a regulatory monopoly to the FDA is creating a significant obstacle to Americans' timely access to new medicines.

Therefore, Congress should amend the Food, Drug, and Cosmetic Act to allow Americans to use new medicines once the EMA has removed its prohibition. The FDA would retain the power to compel manufacturers to label their medicines with the warning that the FDA has not yet approved their safety or efficacy.

After five years, Congress would review how Americans have responded to the lower regulatory cost and faster availability of new medicines due to these amendments and introduce further regulatory reform based on that information. This review might result in increasing regulatory competition even more by turning the FDA into a "certifier of certifiers," which would allow private-sector certifiers to compete to assess new medicines.

While these reforms are radical and long term, patients with life-threatening illnesses who currently have no treatment options need immediate regulatory relief. This relief would become available via the policies enshrined in the Compassionate Access Act, introduced last year by Representative Diane Watson (D-CA). This law would allow seriously ill patients who have exhausted other treatments to try experimental drugs at an earlier phase of regulatory approval than is possible now, and it would encourage the FDA to use measures other than placebo trials to determine the safety and efficacy of those drugs.[1]

A GROWING BURDEN:
The Federal Monopoly of Pharmaceutical Regulation

For more than a century, the federal government has taken discrete and forceful steps to impose a monopoly on pharmaceutical regulation. Executed through the Food and Drug Administration (FDA), this monopoly has evolved through three functions.

First, the law that founded the FDA in 1906 gave it the authority to oversee the purity of medicines, but did not require manufacturers to get the FDA's permission to market their drugs. A drugmaker was considered innocent until proven guilty of producing and marketing an adulterated medicine.

Second, a new Food, Drug, and Cosmetic Act passed in 1938 gave the FDA the power to determine that drugs were "safe for use," which has a broader meaning than "pure." A product can be both pure and unsafe. On the other hand, "safe for use" is legal language that has no precise meaning. The 1938 act forced manufacturers to submit an application to the FDA, but the law asserted that the FDA had approved by default if it did not request more information within 60 days, after which it had another 120 days to decide to forbid the medicine.

Third, the FDA received further authority in 1962 to determine a drug's "effectiveness," another controversial concept. As the FDA's authority grew from 1906 to 1938 to 1962, it became more difficult to justify the argument that it was exercising legitimate government power instead of undue government interference in private choices.[2] The 1962 amendments gave the FDA the power—indeed, the obligation—to prohibit patients' use of new medicines automatically until the agency gives its permission. By contrast, the initial draft of the Food, Drug, and Cosmetic Act of 1938 did not give the FDA the power to approve new medicines. It merely extended the policing powers (to prosecute after the fact) that the FDA had enjoyed since 1906, so that they now encompassed "safety" as well as "purity." A new drug, however, with an untested solvent (diethylene glycol) killed more than 100 people within a few days while the bill was working its way through Congress, causing a public outcry.

Congress therefore changed the bill to require drugmakers to submit a New Drug Application (NDA) for approval by the FDA

In 1962, however, Congress passed amendments that drastically increased the regulatory costs of researching and developing new medicines.

before introducing a new medicine into interstate commerce. At that point, the NDA was required to demonstrate safety but not effectiveness, and the law required the FDA to take deliberate action to stop a drug from being made available to Americans, rather than allowing FDA inaction to prevent it from becoming available, as later became the case.[3]

The 1938 act and its 1906 predecessor were effective in authorizing the government to act against those who marketed adulterated or misbranded drugs.[4] In 1962, however, Congress passed amendments that drastically increased the regulatory costs of researching and developing new medicines. The 1962 Kefauver-Harris amendments required affirmative, pre-market approval. That is, the absence of response by the FDA no longer passively signaled its approval of a new medicine. These amendments further required that manufacturers receive the FDA's approval before any human testing could occur, or any advertisement or label be put before the public.

The amendments also gave the FDA authority to regulate production by promulgating Good Manufacturing Practices (GMP). Most importantly, the 1962 amendments required that drugmakers demonstrate that a new medicine was "effective" as well as "safe." This significantly increased the costs of regulation and fundamentally changed pharmaceutical research. Research output collapsed, as measured by the number of applications to begin clinical testing for new chemical entities (NCEs).[5] As in 1938, it was an immediate scandal that gave impetus to these reforms.

THE PACE OF NEW DRUG APPROVALS IN THE UNITED STATES LAGGED SIGNIFICANTLY BEHIND THAT OF EUROPEAN COUNTRIES.

The 1962 amendments had languished in Congress until the negative effects of thalidomide, a sedative prescribed to pregnant women, became apparent. In 1958, Richardson-Merrell, an American company, had licensed thalidomide from its German manufacturer for distribution in the United States. Richardson-Merrell submitted an NDA to the FDA in November 1960. The FDA's examiner, Dr. Frances Kelsey, later reported that the company contacted the FDA 50 times in its efforts to get the NDA approved. However, Kelsey had heard reports from Europe that the drug caused nerve damage (to the pregnant women, not their fetuses), and accused the company of withholding information from her. Richardson-Merrell responded by threatening to sue the FDA. Before the drug was approved in the United States, further bad news came from Europe, this time linking thalidomide to birth defects. This increased public support for more regulation and added momentum to the amendments moving through Congress.[6]

Today, thalidomide is often held up as an example of why we need more testing before a government lets patients use a drug. What it actually shows, however, is the limits of pre-market testing. After the birth defects were observed, subsequent trials conducted on the most commonly tested animal species, which were designed to replicate thalidomide's consequences in humans, generally failed to create the birth defects.[7] This indicated that even "gold standard" research protocols would never have uncovered the problem.

The increased regulatory burden in the United States had the effect of slowing down the time it took the federal government to lift its ban on new medicines, especially relative to other countries. By the 1980s, a number of scholarly and other interested observers realized that the pace of new drug approvals in the United States lagged significantly behind that of European countries.

THE INTERNATIONAL CONTEXT

With the development of the European Union (EU), manufacturers gained multiple avenues for lifting the ban on their medicines. Before 1987, all European countries conducted their own regulatory reviews. As far back as 1983, however, the EU introduced pathways for mutual recognition of its member countries' licensing. Although national agencies still exist, increased harmonization within the EU resulted in the 1995 creation of the London-headquartered European Medicines Evaluation Agency. (Because "Evaluation" was subsequently dropped from the name, this study uses the more recent acronym, EMA.) The EU also amended procedures for mutual recognition, whereby the EMA serves a quasi-judicial function: if a member did not recognize another member's approval of a medicine, then the EMA could make a binding decision. However, if a manufacturer submitted its drug application directly to the EMA's Committee on the Propriety of Medicinal Products, which has two representatives from each member state, it did not also have to submit to a national regulatory agency.

The original standard for review was that the EMA's experts submit their recommendation to the European Commission within 210 days, and that the commission make its decision on approval within 90 days after that.[8] Drugmakers were free to seek approval through different regulatory routes, and this created competition for user fees among those regulatory agencies.[9] However, the EMA has increasingly centralized its authority over the years.

In 2003, the EU decided that biological therapies, as well as classical pharmaceutical therapies, for AIDS, cancer, neurogenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases should all come under the central review of the EMA.[10] By 2004, the EMA had instituted a framework for approval that largely replicated that of the FDA. This involved standard review for most drugs and priority review for more important ones, as well as accelerated approval based on surrogate endpoints for drugs that look exceptionally promising, and orphan designation for drugs with very small markets, which therefore need special incentives to motivate investment.[11]

One continuing difference between the jurisdictions is that the EMA chooses reviewers from an external, multinational pool of qualified persons, whereas the FDA reviews new medicines "in house."[12] The FDA has experimented, weakly, with third-party reviewers for medical devices, but not drugs.[13]

THE EMA CHOOSES REVIEWERS FROM AN EXTERNAL, MULTINATIONAL POOL OF QUALIFIED PERSONS, WHEREAS THE FDA REVIEWS NEW MEDICINES "IN HOUSE."

Because of increasing delays in patients' access to new medicines, the UK, Sweden, and Germany restructured their regulatory agencies and increased funding, from user fees rather than general taxation, starting in the late 1980s.[14] This was meant to increase the resources dedicated to regulatory approval. As discussed later, the United States did the same starting in 1992 in order to speed up the approval of new medicines relative to the EU.

The most obvious effect of a government ban is that it takes longer for patients to get new prescription drugs.

Once all relevant regulatory authorities had locked in funding through user fees, a certain degree of convergence took place, both in timing of approvals and in operations. Indeed, the FDA and EMA have increasingly collaborated on means to increase communication between the two agencies and sponsors, thereby avoiding duplicative testing. In January 2005, they formalized a pilot program that participants deemed successful.[15] Since 2003, the FDA has had a similar arrangement with SwissMedic, its counterpart in Switzerland.[16]

Last year, the FDA and EMA began an 18-month pilot program to share information concerning Good Clinical Practices focusing on a number of issues, including inspection of sites where clinical trials take place.[17]

DRUG LOSS AND DRUG LAG

The most obvious effect of a government ban is that it takes longer for patients to get new prescription drugs. Scholarly research on the effects of increased government intervention goes back to the 1970s in the United States, driven by the suspicion that the 1962 FDA amendments, which imposed the new requirement of "efficacy," had slowed the pace of innovation and the introduction of new medicines. Researchers have coined two terms to describe the consequences of the increased regulatory burden: drug loss and drug lag.

The requirement that a pharmaceutical innovator demonstrate efficacy, in addition to safety, to the government is very expensive. Even if clinical trials only involve testing a new drug against a placebo for effectiveness, trials are costly because they are conducted on sick patients, whereas testing for safety is done on healthy subjects, who are easier to enroll. By the beginning of the twenty-first century, it was taking 60 or more clinical trials covering almost 6,000 subjects to meet the FDA's requirements, which now result in only one new drug in 10,000 overcoming all the research, development, and regulatory hurdles.[18]

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Drug loss is the more difficult of the two problems to measure, but is probably also the more detrimental to patients' long-term well-being. It refers to the fact that the increased burden of regulatory compliance reduces the productivity of research and development (R&D). Every dollar invested in R&D produces

less benefit for patients because more of that capital is spent to satisfy bureaucratic requirements that not all patients value. Most of the research on drug loss has considered the effects of the 1962 amendments to the Food, Drug, and Cosmetic Act.

In 1976, *Economic Effect of New Drug Regulation in the United States*, a staff report for a government inquiry on the effect of the amendments, determined that manufacturers launched an average of 42 new chemical entities (NCEs) annually from 1950 through 1962, but an average of only 14 a year from 1963 through 1975.[19] A decade after the amendments, professor Sam Peltzman analyzed their effect. He determined that NCEs introduced annually during the period 1963 through 1970 were only 39 percent of the number introduced annually during 1951 through 1962. Peltzman's analysis demonstrated that patients' demand for new medicines had not changed over that period. He therefore attributed the drug loss to the increased regulatory burden of the 1962 amendments. He also determined that the drugs lost would have been as effective as those that survived.[20]

U.S. GOVERNMENT POLICY WITH RESPECT TO IMPROVING THE QUALITY OF INFORMATION ABOUT MEDICINES IS, UNFORTUNATELY, HIGHLY RESTRICTIVE.

The only other economic analysis of the 1962 amendments in the 1970s was an unpublished doctoral thesis by James Jondrow, which challenged Peltzman by arguing that the 1962 amendments killed ineffective drugs, not effective ones.[21] The FDA's own calculations, however, showed "important" NCEs dropping from 6.23 to 3.73 annually from the first period to the second.[22] Although Jondrow and others have criticized Peltzman, none has offered a satisfactory competing explanation for the drug loss. Peltzman's critics only challenge his argument that all the drug loss was due to the 1962 amendments. None denies that the amendments caused some of the drug loss.[23]

The 1980s saw new research, more specifically on the effects of the 1962 amendments on the productivity of R&D. Professors Henry Grabowski and John Vernon criticized Peltzman's estimates because he employed the concept of consumer surplus to estimate the demand for medicines, which Grabowski and Vernon considered inappropriate. They argued that it is difficult to generate a meaningful classical aggregate demand function because patients themselves do not select the prescription drugs they use. Nevertheless, using different methods and data, Grabowski and Vernon found that drugmakers faced a serious decline in R&D productivity from 1962 to 1975, as measured by the ratio of the number of patents to the number of R&D employees. The reduction was more than one-half.[24]

Perhaps a more subtle effect of the regulations was the reduction in competition caused by the high cost of regulatory compliance. Professor Lacy Thomas found that the 1962 amendments had a devastating impact on small pharmaceutical firms and their ability to conduct R&D, thus entrenching larger firms. She also found that innovation did not decline for larger firms, a finding that differs from those of other studies.[25]

This consequence of the 1962 amendments may explain why today's brand-name drugmakers do not lobby for drastic reform, such as repeal of the 1962 amendments or even abolition of the FDA and other countries' regulators, which impose such large costs upon them. Rather, they support hefty user fees as long as the FDA approves drugs within a certain period. The excessive regulation imposes a greater proportional cost on smaller companies than large ones; therefore, the large ones are more likely to favor it. Further, the fate of the smaller companies that survive depends on the favor of the regulatory

In the United States, the average review time rose from less than two years to more than three years between 1962 and 1989, while average testing time (before submitting a new application for review) rose from three years to between six and seven years.

bureaucracies. Therefore it would not serve them, acting individually, to attack vigorously the FDA and its counterparts in other countries.[26]

Another facet of the problem of drug loss is that the costs of regulatory compliance are fairly fixed, no matter the number or incomes of the relevant patients. This means that manufacturers will necessarily pull back from R&D on smaller markets. Thus, "minorities" stand to suffer more from drug loss.[27] One approach to rectifying this in the United States is the Orphan Drug Act, which gives greater protection of intellectual property to medicines targeted at smaller groups.

Perhaps because there have been great therapeutic advances in new prescription drugs, and perhaps because the patients, doctors, research-based pharmaceutical industry, and other interested parties have just gotten used to the status quo, subsequent research tended to focus on the more easily measurable problem of drug lag.[28]

Drug lag is usually defined across countries, measuring how much longer it takes for one country versus another to remove its ban on a new medicine. As noted previously, American observers coined this term for our country's increasing lag versus European nations after the 1962 amendments were passed.

In the 1970s, a number of analysts examined the growing drug lag between the United States and other countries, mostly European countries but also Canada for some periods. The FDA continued to assert that there was no drug lag, even though it is not difficult to measure.[29]

Indeed, evidence showed that in the United States, the average review time rose from less than two years to more than three years between 1962 and 1989, while average testing time (before submitting a new application for review) rose from three years to between six and seven years.[30] The publication of studies that demonstrated the growing drug lag between the United States and Europe helped to motivate demands for improvement in the United States.[31] Other, more dramatic events also focused public attention on the FDA's role in denying patients the ability to get medicines they needed.

One impetus for FDA reform was the role of gay activists in calling attention to the bottleneck holding up AIDS drugs. In October 1988, gay activists staged a large rally outside FDA headquarters, accusing the FDA of causing deaths and demanding that patients have input into regulatory decision making. One scholar has argued that gay activists were more successful than other patients' groups in pushing back the government because they had already organized a movement to achieve political and cultural change, better preparing them to challenge the state when the virus hit their community.[32]

All this talk of "drug loss" and "drug lag," of course, invites an understandable response from certain quarters.

INCENTIVES IN A REGULATORY MONOPOLY:
Slow Does Not Equal Safe

Maybe we *should* lose some drugs, the reasoning goes, or let their approval lag. After all, some medicines have dangers of which regulators and other interested parties are unaware. There are many stories of the FDA approving drugs that subsequently demonstrated unexpected negative effects. On the other hand, if the FDA permits a drug, nobody is obliged to use it. Its use can be corrected "downstream," as new information about the medicine's effects is learned in practice. This is not the case if the FDA forbids it.[33] In a politicized environment, this imbalance introduces seriously skewed incentives for overly cautious regulation.

Standard arguments in favor of regulation start from the position that individuals are poorly informed. This idea is well developed in neoclassical economic theory, and includes non-intuitive insights, such as that people can remain poorly informed even if they think that they have fully and effectively searched for information.[34] Common sense also tells us that people are not capable of learning as much about medicines as the drugmakers know. It is not easy to learn about the effects of medicines, so most individuals (including doctors) will be greatly less informed than the manufacturer that wants them to use a given medicine. It is also costly for patients to inform themselves, so manufacturers will not be motivated to communicate risks to them fully. There is a critical difference, however, between banning a medicine and improving the availability of information about it.[35]

U.S. government policy with respect to improving the quality of information about medicines is, unfortunately, highly restrictive. The government bars patients from buying most drugs on their own (without a prescription), allows physicians to prescribe only from an approved list, and prevents drug companies from disseminating information that the government has not censored.[36] Thus, actual government policy reduces patients' ability and incentives to become informed and thereby prevents information from disciplining the pharmaceutical market.[37] As with the government banning the use of new medicines, restricting the information manufacturers may disseminate about them does not guarantee that better information will fill the vacuum. We simply face a choice of low or zero levels of (self-described) "unbiased" information from the state or other interest groups, versus high levels of "biased" information from drugmakers.[38]

The costs of bad choices in health care are high, and the benefits of good choices are huge. We would therefore expect patients, their loved ones, and caregivers to invest lots of effort in learning about a possible therapy. Similarly, we would expect intermediaries to intervene to lower the costs to patients of obtaining high quality information. In other areas, individuals face poor information and serious consequences if they make bad decisions, but the government leaves them alone to decide. Despite poor information, individuals nevertheless make better decisions than government agents would on their behalf, because individuals face the consequences. Consider marriage: choosing a partner is fraught with risk, yet the government lets adults decide for themselves.[39]

THE COSTS AND BENEFITS OF FDA REGULATIONS DO NOT ACCRUE TO SOCIETY AT LARGE, BUT TO SPECIFIC INDIVIDUALS.

Those who must rely on hypothetical benefits in the debate about new drugs are at a distinct disadvantage against those who can point to real and dramatic evidence of the harm that drugs occasionally do.

Although banning drugs, as the government currently does, might benefit the ill-informed, patients overall would benefit even more from warning labels stating that regulators "would not yet have approved" the drug if they had the power to withhold approval. This is because informed patients could then use the drug, and the ignorant or more risk-averse ones would shy away from it.[40] And abolishing the ban would not create an equal and opposite effect: the government would not force any patient to use a drug that he or she would prefer not to take.

Certainly, studies of government-mandated warnings on items such as seatbelts, alcohol, and cigarettes have found little if any effect. Although some have argued that this is because of the high cost of dealing with warning labels, effects are small even when individuals have read and understood the labels.[41] This could be because the government agents who mandate the warning labels overestimate people's demand for such warnings, or because people actually get no new information from them.

If regulators who have the power to regulate information compel private agents to be too risk-averse in their communications, it is likely that the same will occur when regulators get the power to ban products. Even estimating the net effect of such regulation is extremely challenging. It assumes that there is a social good that can be measured by trading off lives lost versus lives saved. But this cannot really be done given that different individuals are willing to undertake different risks.[42] Such analyses are reported in this paper, but only because the government has socialized the issue by automatically banning new medicines, forcing otherwise unnecessary trade-offs among different groups of patients.

Even if two patients have exactly the same, accurate understanding of the risks and benefits of a given medicine, one may choose to take it and the other to avoid it, because the latter is more averse to the risk and values the benefits less. Therefore, the costs and benefits of FDA regulations do not accrue to society at large, but to specific individuals with different needs. For example, patients with terminal diseases often demand new therapies faster than regulators can approve them, because the cost of failure to those patients is very low.[43] Indeed, if a person is so ill that the likelihood of death without treatment is 91 percent, a rational person will willingly undertake a treatment with a 90-percent risk of death.[44]

The cost to the government and its agents of allowing patients to use the medicines that the patients think they need can be high, especially in a democracy. The majority of Americans are not affected by the government's decision to ban any single new drug. They do, however, exert political pressure. The poorly informed majority will not experience the consequences of its influencing the government to impose more intervention and regulation. Especially in a crisis, however, this majority will motivate the government to make decisions that reduce the welfare of affected patients, unless a very determined minority, such as the gay patients noted earlier, is able to resist.

So, incentives facing the government regulators who are supposed to manage pharmaceutical risk on behalf of patients lead them to impose too much safety (of one type) by denying "risky" products.[45] Unfortunately, this often harms patients' welfare. To combine the language of bureaucratic incentives with that of statistics, the FDA can make two types of mistakes.

A Type I error occurs if the regulators approve a product that later proves to have such negative consequences that it is pulled from distribution. A Type II error occurs when the regulators deny approval for a medicine that would have had net beneficial effects on patients' health. These two errors both have negative consequences for patients, but the consequences to the government and its agents are different. The public receives different information about the two types of wrong decisions.

A Type I error incites the wrath of the media and deploys a focused public against government agents. Take, for example, the following statement introducing a decade-old article on drug safety in *BusinessWeek*: "It is almost a grim routine by now: After the Food and Drug Administration gives the go-ahead for a new drug, the product is yanked from the market when some unforeseen problem arises."[46] This claim is extremely dramatic by any reasonable standard.

> Delaying these drugs by just one year cost 37,000 to 76,000 lives per decade in the U.S. population.

Type I errors are not as clear-cut as we are tempted to think. The FDA generally assesses "safety" and "efficacy" against a placebo, but this reveals limited information because, although the subjects' median response to the drug may be the same as to the placebo, there will be variation that is not just statistical "noise." People are heterogeneous in their response to medicines, and researchers may not identify these differences as a source of the variance in outcomes.[47]

On the other hand, Type II errors, when the regulators deny approval for a beneficial medicine, both harm patients in the short run and reduce competition in a given therapeutic area in the long run by squelching research and development. The public is unlikely to be aware of such errors. Only companies and researchers that have been harmed by the error will concentrate on the issue. In the absence of an energetic group of advocates for affected patients (such as the gay community), public opinion is unlikely to be inflamed, because nothing has changed from what existed before. The loss to patients is not nearly as obvious as it is for Type I errors.[48]

Indeed, the public at large and even many physicians are unaware of what new medicines are available. They are even less aware of which drugs are not being invented (are being lost) because of regulatory biases. When a drug that might have benefits is abandoned, we have only uncertainty and a lack of information. Even if a new drug would reduce mortality from 30 percent to 20 percent, no one can predict who will belong to the 10-percentage-point gap. Therefore, the earlier the government kills a promising new drug, the more difficult it is for potential beneficiaries to identify themselves and organize to resist the government's interference. If an approved drug kills someone, however, the victim is clearly identified.[49]

> The drug lag cost many thousands more American lives than it saved... no matter how long the drug lag, it can never ensure that the FDA allows only "perfect" drugs into circulation.

Of any large sample of drugs that start development, a number will have been abandoned because of ineffectiveness or harm. Of those eventually marketed, there will be both benefit and harm. We do not know what benefits the abandoned drugs might have provided because their manufacturers obviously

cannot communicate those benefits.[50] As one policy analyst has said of the uphill battle to motivate the general public to resist pharmaceutical overregulation, "Those who must rely on hypothetical benefits in the debate about new drugs are at a distinct disadvantage against those who can point to real and dramatic evidence of the harm that drugs occasionally do."[51]

Lengthening the time new medicines are automatically banned only retards the production of new information about their possible adverse effects in the population.

Politicians are usually not physicians or scientists. Therefore, they are highly subject to information asymmetry, and they are likely to accept the FDA's advice. Unless it carries a high cost politically, politicians really have no incentive to seek out contrary information. On the other hand, the FDA Commissioner his subordinates are compelled to justify their actions in front of congressional committees. Tension between the executive and legislative branches has caused congressional agencies to conduct many studies on the effects of the FDA's growing regulatory burden.[52] Nevertheless, there is no reason to believe that this struggle between equally unscientific political interests will result in regulatory decisions that serve the public interest.

Peltzman, discussed earlier, estimated that the costs of delays in patients' use of new medicines caused by the 1962 FDA amendments were far greater than the benefits derived from avoiding side effects. Having calculated the drug lag, using econometric tools, he estimated that the delay cost patients $350 million to $450 million in lost benefits, in exchange for about $100 million worth of adverse events avoided, a net loss of about four to one from 1963 through 1970.[53]

A decade later, at the peak of U.S. drug lag, Dale Gieringer of Stanford University examined the consequences for mortality of the FDA's lengthy drug-approval times. This approach has the benefit of not requiring an estimation of how much other people value their health, but simply works with the reasonable assumption that most people would prefer to be alive rather than dead. Gieringer looked at the differences in casualties from prescription medicines between the United States and less regulated countries, and compared that to reductions in mortality from diseases where drugs are known to play a major role in improving outcomes. His analysis concluded that the costs of delayed drug approval in the United States far outweighed the benefits of such delays.

Examining new drugs introduced in the United States between 1950 and 1977, Gieringer concluded that the new medicines had the gross effect of reducing mortality by somewhere between 50 and 102 lives per 100,000 (or a range of 43 to 88 lives per 100,000 if tuberculosis is excluded). Therefore, delaying these drugs by just one year cost 37,000 to 76,000 lives per decade in the U.S. population (or 32,000 to 65,000 excluding tuberculosis). The actual drug lag of between eight and 19 months led to the conclusion that the ban cost between 21,000 and 120,000 American lives per decade. However, Gieringer recognized that this estimate is likely somewhat positively biased because of other factors that affect the uptake of new drugs by patients.

For example, hypertensive patients were unlikely to learn the benefits of drugs for their condition during the period, because the federal government generally prevented drugmakers from communicating this valuable information to them.[54] On the other hand, because the analysis addressed only drugs that manufacturers actually launched during the period, it could not estimate the benefits that patients did not enjoy because of the drug loss due to the 1962 amendments. Gieringer did not ignore the fatal effects of a few of the drugs that the FDA did allow onto the U.S. market.

From 1950 to 1980, 11 drugs were introduced that were to be implicated in more than 100 deaths or serious adverse events worldwide. The biggest killer was isoproterenol, associated with 3,500 asthma deaths in children. Thalidomide was related to more than 10,000 birth defects.[55] These tragic outcomes, however, were overwhelmed by the benefits of other medicines approved during the period. Because the FDA took longer to approve new medicines than other countries' regulators did, it saved an estimated 5,000 to 10,000 lives per decade during the period by preventing Americans from using a handful of medicines.[56] Although the wide ranges of lives both lost and saved prevent us from calculating a meaningful ratio, Gieringer's analysis suggests that the drug lag cost many thousands more American lives than it saved, a conclusion similar to that expressed in dollars by Peltzman. Subsequent research has confirmed the value of medicines developed during the period of growing drug lag, indicating that the lag was impeding faster adoption of effective new therapies.

Not all of our increased life expectancy in recent years is due to prescription drugs, but much of it is. For example, a number of innovations in treatment have contributed to superior outcomes after heart attacks in the United States. From 1984 to 1998, the life expectancy for elderly heart-attack patients increased by one year, even though the frequency of heart attacks stayed about the same. Between 1975 and 1995, about one-third of the increase in life expectancy for heart-attack victims was due to increased use of aspirin, a drug invented and marketed in the 19th century ~~w~~hen there was no regulation of pharmaceuticals. Surgical procedures (such as angioplasty) reduced the likelihood of death within two years by about a quarter. However, about 17 percent of the reduction was due to clot-busting drugs introduced during and since the 1970s.[57]

In an extremely thorough analysis of international data on health spending, professors H. E. Frech and Richard D. Miller Jr. looked at pharmaceutical consumption in 1990 and its effect on mortality five to 10 years later, controlling for other variables such as obesity, smoking, alcohol consumption, and national income.[58] Overall, they found that increasing per capita pharmaceutical spending by 10 percent would increase life expectancy by 0.3 percent at age 40 and 0.6 percent at age 60. For the United States, one extra dollar spent on prescription drugs would have added 1.87 days to life expectancy for a woman aged 40, and 2.11 days for a woman aged 60. For men, the corresponding number of added days of life was 1.64 and 1.76. Scholars who study the effects of health spending also like to understand what it does to the quality of years added, which is called Disability-Adjusted Life Expectancy (DALE). DALE increased by 2.05 days for each dollar spent on prescriptions for 40-year-old women, and by 2.51 days for 60-year old women. For men, the corresponding additional days of DALE were 1.76 and 2.04.[59]

Looking at it another way, Frech and Miller found that the lifetime cost of pharmaceutical spending to add one year of life expectancy was $15,952 for a 40-year-old woman in the United States, and $14,486 for a 60-year-old woman ($11,558 for DALE). The lifetime cost of adding one year of life expectancy was $17,099 for a 40-year-old man, and $16,581 for a 60-year-old man ($13,571 for DALE), well below the threshold of cost-effectiveness that most health economists use to measure value for money.[60]

Drilling deeper into specific categories of disease, Frech and Miller found that the effects of pharmaceutical spending were positive for circulatory diseases, in both the elderly and those suffering prematurely, and for cancer and respiratory diseases in the elderly.[61] Further, no matter how long the drug lag, it can never ensure that the FDA allows only "perfect" drugs into circulation. Indeed, FDA reviews add no available information, because they consider only research that has already been completed. Some serious side effects do not become apparent until after a drug has been approved and used more widely by the public.

A 1990 analysis by the U.S. government auditor reported that of 198 drugs approved by the FDA between 1976 and 1985, 102 (52 percent) had serious risks—including side effects that could lead to hospitalization, severe or permanent disability, or death—that were determined only after the FDA had approved them. These led to changes in labeling that limited the appropriate populations, or added warnings or precautions.[62] All but six of these drugs, however, were still marketed as of September 1989. This is because, as the report noted, "the number of serious post-approval risks is small when compared to the number of adverse reactions that had been identified at the time of approval."[63] Nonetheless, while recognizing the risks of poor prescribing and adverse events, the U.S. Department of Health and Human Services was horrified by the report, fearing that it would alarm patients and cause them to avoid valuable medicines.[64]

Unfortunately, politicians often respond to newly discovered information about the risks of a medicine by calling for even more testing, on all medicines, before bans are lifted. Such calls ignore the diminishing marginal utility of testing. The most valuable information about a new medicine is that subjects did not drop dead on the first day of a clinical trial.[65] This first hurdle is also relatively cheap to clear. More testing for safety and efficacy comes at increasing marginal cost for less marginally valuable information. Nor is the government capable of knowing how much information each patient wants, nor at what cost. If manufacturers were forced to do only the degree of testing that patients required, we would expect them to start selling their new medicines earlier and continue testing subsequently, in the hope of eventually capturing patients who are more risk-averse than the initial users.

Lengthening the time new medicines are automatically banned only retards the production of new information about their possible adverse effects in the population. No matter how encompassing a clinical trial is, there is no way that it can determine every possible risk that patients will face once the general population starts using the drug. Testing according to government regulations is already very expensive. For a trial of 2,000 to 3,000 subjects, only adverse drug reactions (ADRs) occurring in at least one in 1,000 cases will be considered significant. A trial would need 16,000 subjects to have an 80-percent chance of identifying all ADRs occurring in one in 10,000 people.[66] Once the FDA approves a drug, it will likely be used by millions of people. We can never be certain that we have learned every risk about a medicine until the last person on earth has taken it.

RECOVERING FROM DRUG LAG:
PDUFA to the Rescue

The research discussed previously was among the influences that led Congress to pass a law in 1992 that changed how the FDA was funded. By adding user fees, paid by drugmakers to have their medicines licensed, to funding from general taxation, the Prescription Drug User Fee Act (PDUFA) was designed to increase the FDA's resources and speed up its approval processes. PDUFA expires every five years, and Congress has successively renewed it without interruption as part of more comprehensive FDA modernization bills; PDUFA IV passed in 2007. There is no doubt that it is associated with faster regulatory approval. According to one academic analysis, mean approval times for all drugs approved between 1984 and 2001 dropped from more than 30 months before PDUFA's passage to 16.8 months subsequently.[67]

According to the U.S. government's auditor, median approval time dropped from 27 months in 1993 to 14 months in 2001.[68] According to the brand-name drugmakers' trade association, the Pharmaceutical Research and Manufacturers of America (PhRMA), PDUFA cut average (rather than median) review time from 30.2 months in 1991 to 16.9 months in 2003.[69] Another scholarly study of new substances approved from October 1979 through September 2002 came to similar conclusions. This highly sophisticated model concluded that time to approval declined between 6 and 7 percent because of PDUFA I (September 1, 1992, to September 30, 1997) and between 3 and 4 percent because of PDUFA II (October 1, 1997, to September 30, 2002). Approval for AIDS drugs (during the entire period) was much faster than for other categories of drugs or biologics.[70]

Significantly fewer drugs would have been approved in the absence of PDUFA: 55 in 1996 versus 62 actually approved. If PDUFA I (1992) and PDUFA II (1997) had not been in effect during the decade, only 376 new drugs would have been approved, instead of 389, leading to negative consequences for many patients.[71]

This improvement in the FDA's performance is also apparent in international comparisons. Indeed, drug lag is no longer an issue for the United States, as shown in table 1. In 1996, the United States became the first market for more than half of the new prescription drugs approved by the FDA.[72]

Table 1: Time to Approval for New Drugs in Five Countries, 1999–2001			
	Number of New Drugs Approved over Three Years	Median Time to Approval (Days)	Lag versus U.S. (Months)
Canada	78	645	9.0
Australia	89	551	5.9
Sweden	89	431	2.0
United Kingdom	71	479	3.5
United States	85	371	N/A
Source: Rawson 2003, p. 1235; author's calculations[73]			

Among the jurisdictions, however, variance remains. During the years 2000 through 2005, the EMA approved 122 new pharmaceutical products. Of these, 113 were approved by the FDA before, during, or after this period. However, the FDA classified only 99 of the 113 as new (as opposed to variations on existing drugs, differing only in dosage, for example). Of these 99, the FDA approved 71 during the period. The mean approval time was almost exactly the same: 15.8 months in the EU versus 15.7 months in the United States. However, 24 of the new drugs (fully one-third) were approved faster in the EU. Those 24 averaged approval in 11.6 months.[74]

By 2007, the time to approval for new, innovative prescription drugs was down to 12.3 months, on average, for 18 new medicines approved by the FDA.[75] Unfortunately, this was the high-water mark of bureaucratic speed. In 2008, the average time to approval lengthened to almost 18 months. The good news is that 24 drugs were approved that year.[76] The brand-name drug makers strongly support PDUFA, rightly associating the law with speedier approval times, which have brought great benefits to American patients.[77] Of course, critics charge that the increase in funding from PDUFA is tantamount to hiring the fox to guard the henhouse, as the FDA is now directly dependent on funding from the brand-name pharmaceutical industry.

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Research indicates that such fears are groundless. In fact, an increase in staffing at the FDA's Center for Drug Evaluation and Research (CDER)—the division responsible for approving new drugs—and a consequent reduction in approval times started in 1986, a few years before PDUFA was introduced in 1992.[78] Indeed, one scholarly study shows that the source of funding had no impact on the pace of drug approvals. An examination of all drug submissions for new substances between 1977 and 2000 revealed a strong relationship between the number of staff employed in the CDER and the speed of review. An increase of 100 in CDER staff was associated with a decline of between 2.6 months and 3.3 months. Increased staff before PDUFA was associated with even more improvement in review times for successful drugs: between 4.56 months and 5.17 months for an increase in CDER staff of 100. Nor did it matter whether the drugs were sponsored by companies with bigger sales or ones that invested more money in lobbying.[79]

Certain interest groups, unfortunately unwilling to appreciate the difference between Type I and Type II errors, have resisted the benefits of PDUFA from the start. One organization that argues against the faster approval times associated with PDUFA is the self-styled consumer advocacy group, Public Citizen/Congress Watch. According to this group, faster approvals occur because the FDA is no longer doing its job adequately, and allowing unsafe drugs into the United States. Public Citizen/Congress Watch reported that nine new medicines the FDA licensed in the eight years 1993 through 2000 had to be withdrawn. In comparison, only five had to be withdrawn in the previous eight years, before the FDA started to receive user fees to fund faster examinations of new drugs.[80] Presented this way, the higher rate of withdrawals certainly appears startling: an increase of 80 percent. A lot of the shock, however, comes from seeing the risk reported relative to the previous period's number of withdrawals, rather than as a share of the drugs approved during the period in question.

One scholarly article, which suggested that the FDA's faster approval times potentially increased the supply of risky medicines, found that of 548 new chemical entities approved by the FDA from 1975 to 1999, 10.2 percent subsequently received black-box warnings or were withdrawn; of these 16 (2.9 percent of the total) were withdrawn. (A "black-box warning" is a notice on the package insert, which warns of serious adverse effects.) The flip side of this is that 90 percent did *not* receive such warnings and a full 97 percent were *not* withdrawn.[81]

Several thousand patients contacted the FDA and the manufacturer after the withdrawal, demanding Lotronex back and furious at Public Citizen/Congress Watch for advocating its withdrawal. Fortunately for them, it has since come back on the market.

U.S. government agencies tend to report withdrawals as a share of the drugs approved in the period in question. The U.S. government's auditor reported that the withdrawal rate for the eight years previous to PDUFA's authorization in 1992 was 3.10 percent, versus 3.54 percent for the subsequent eight years, an increase in withdrawals of less than 0.5 percent of new drugs approved. Some of these were withdrawn because patients and doctors did not use them correctly, rather than because they demonstrated rare side effects not discovered during trials.[82] Examples include Seldane™ (an antihistamine), Duract™ (a painkiller), and Rezulin™ (for diabetes).[83] Even though the increase reported was not very dramatic, the FDA found it necessary to respond to the auditor's report, pointing out that the change was not statistically significant.[84] Further, of the 14 drugs pulled from the U.S. market after the implementation of PDUFA, the FDA had clearly approved three *before* PDUFA came into effect, and two were likely submitted to the regulator before that date.[85]

In another report, the Office of the Inspector General of the U.S. Department of Health and Human Services presented similar figures, shown in table 2. Importantly, this analysis also showed the withdrawal rate according to the fiscal year in which the manufacturers applied to have the ban on their new drugs lifted. This more clearly shows the effect of PDUFA than analyses based on the year of approval. Although the rate increased slightly in the five years after PDUFA, it dropped again the next half decade. Neither of these two nonpartisan reports, however, shows a statistically significant change in withdrawal rates before and after PDUFA. (Also note that both reports use periods of multiple years for analysis. Using annual periods would show zero withdrawals for several years.)

Table 2: Rate of New Molecular Entities Withdrawn from U.S. by Five-Year Period				
Period	1983–1987	1988–1992	1993–1997	1998–2002
Calendar Year of Approval	3.7%	2.5%	3.6%	1.7%
Fiscal Year of Receipt	2.7%	2.6%	3.1%	2.3%
Source: Rehnquist 2003[86]				

Despite the lack of evidence of increased drug withdrawals due to PDUFA, Public Citizen/Congress Watch has argued that many of the FDA's own reviewers think that the performance requirements associated with user fees made the agency too willing to approve new drugs quickly. Two physicians associated with Public Citizen/Congress Watch surveyed the FDA's medical officers a few years after PDUFA's authorization, collecting the responses anonymously to protect the respondents. They reported that 31 percent (53) of the 172 medical officers responded. Of these, 19 reviewers identified a total of 27 drugs that they thought should not have been approved. Twelve reviewers thought that 25 drugs had been approved too fast.[87] However, the number of unsatisfied medical officers responding was really quite small, and subject to sample bias. Subsequent reports of withdrawals (discussed previously) do not support the allegations.

Two subsequent reports by nonpartisan government offices offer more classical complaints by disgruntled public servants. The government's auditor found that since PDUFA, the FDA's reviewers had had their workload increased, had experienced higher attrition than other government agencies, and did not undertake professional development to the degree recommended by the agency.[88] In another survey, to which subjects responded anonymously, some reviewers expressed concerns about the increased speed of approvals and the time pressure since PDUFA. However, 78 percent were confident in the decisions that the FDA had made with respect to a drug's efficacy, and 70 percent were confident in the FDA's labeling decisions. This survey also boasted a response rate of 47 percent, much higher than the survey conducted by Public Citizen/Congress Watch.[89] According to a 2009 survey, more than half of FDA managers believed that the FDA was making great progress in communicating product safety information to the public.[90]

Indeed, even the banning of a drug after previously unknown hazards have become apparent is fraught with risk, despite the headline risk to the FDA's reputation once the media sink their teeth into it. One example is Propulsid™ (cisapride), a widely used gastrointestinal drug withdrawn in 2000 because of a small number of catastrophic effects, even though it benefited many patients. In Canada, for example, Propulsid was associated with 44 reported cardiac arrhythmias, out of a total of 7.7 million prescriptions. Since 1990, 80 deaths had occurred in the United States and Canada that were associated with use of the drug.[91] Unfortunately, its removal caused other patients, for whom Propulsid was very beneficial, to suffer. The press reported the story of one patient who could no longer digest without pain. The FDA now allows such patients to continue to use Propulsid, but only under certain criteria and while enrolled in special studies.[92] This case is a sterling example of the bias toward Type II versus Type I errors in the regulatory regime.

Another example is Lotronex™ (alosetron HCL), used for irritable bowel syndrome. The manufacturer took Lotronex off the market on November 28, 2000, at the FDA's urging. About 300,000 patients were taking the drug, and the FDA responded to reports of 70 cases of severe constipation or ischemic colitis

(lack of blood flow to the colon), from which five deaths occurred. Several thousand patients contacted the FDA and the manufacturer after the withdrawal, demanding Lotronex back and furious at Public Citizen/Congress Watch for advocating its withdrawal.[93] Fortunately for them, it has since come back on the market.

Other examples abound. Vioxx™, one of the Cox-2 inhibitors often described as "super-aspirins," was withdrawn in 2004 in a storm of media outrage and litigation over an increased number of heart attacks in patients using it. Research data suggested an increased risk of suicidal "ideation" among children and adolescents taking a certain class (SSRI) of antidepressants. Meta-analysis of Avandia™, a diabetes drug approved back in 1999, indicated an increased number of heart attacks and strokes in its users. All of these conclusions were more tentative than the climate of public opinion suggested.[94]

Despite speedier approval, the FDA still harms patients by needlessly delaying their legal access to new medicines.

The withdrawal of any drug results in a flurry of litigation, much of which is notorious for plaintiffs' lawyers' emotionally manipulating juries to focus on heart-wrenching testimony of harm to the exclusion of evidence of a medicine's benefit. After the first product-liability trial for Vioxx™, one juror told the media, "Whenever Merck [the manufacturer] was up there, it was like wah, wah, wah" like the adults outside the panel of a *Peanuts* cartoon. Another told the media that he had wanted to punish Merck for perceived disrespect that the company had toward him. Yet another considered it an "admission of guilt" that Merck's chief executive officer did not testify in person, but via videotape instead.[95]

These examples are given not to make a layman's argument that health professionals and patients should ignore the serious risks associated, albeit infrequently, with these and other medicines. The purpose, rather, is to point out that increasing the quantity and quality of information about a drug is not at all the same as simply imposing a government ban on its use.

Finally, research conducted using data after the implementation of PDUFA confirmed the net benefit of medicines that had been approved faster. Professor Frank Lichtenberg of Columbia University examined U.S. data from 1960 to 1997, and estimated a health production function with a number of inputs. As a proxy for medical innovation, he used the number of approvals of new drugs by the FDA. The results showed that an increase in the approval rate of one drug per year explains an increase in life expectancy at birth of 40 days (0.093 year).[96]

Subsequently, Lichtenberg looked at new drugs introduced after 1990 and after 1993 and at outcomes for diseases specific to those drugs from 1990 to 2003: potential years of life lost at age 65 and age 75, hospital admissions, hospital discharges to long-term care facilities, and deaths in hospital. Except for deaths in hospital, all outcomes improved. Most notably for our purposes, Lichtenberg concluded that potential years of life lost, which the Centers for Disease Control and Prevention reported as 8.3 million before the age of 65 in 2002, would have been 1.6 million more if no new drugs had been introduced since 1990. Potential years of life lost before age 75, which were actually 15.4 million, would have been 1.7 million more. Looking at the total potential years of life lost over the period 1990 through 2002, Lichtenberg concluded that 6.2 million more would have been lost before the age of 65 and 7.4 million more lost before the age of 75 in the absence of new drugs.[97] Clearly, even a short delay in introducing new drugs costs lives.

Lichtenberg also determined the effect that spending on newer drugs had on other health spending, looking at U.S. data for the three years from 1996 through 1998. He found that a reduction in the vintage of a drug reduced non-drug medical expenditure by 7.2 times as much as the increased spending on the drug. For example, using a drug that was only 5.5 years old, instead of one that was 15 years old, decreased non-drug health spending by $129 per patient, even though it increased prescription spending by $18 per patient (because new drugs typically are higher priced than old ones). Most of the savings were due to reduced spending on visits to hospitals ($80) and physicians' offices ($24).[98]

Professors Lichtenberg and Virabhak, examining U.S. data from 1997, estimated a number of effects of using new drugs on various indicators of quality of life. Generally (but not universally), these models found that using newer drugs increased patients' health status, while reducing physical limitations and limitations on social and other activities. Most of the models also determined that using new drugs increased the likelihood of patients' living another year.[99]

Most recently, Lichtenberg examined two sources of innovation in cancer treatment for the period 1996 through 2006: improvement in diagnostic imaging and new drugs. While 40 percent of the decline in cancer mortality was due to better imaging technology, one-quarter was due to pharmaceutical innovation. Combined, these two effects explain an increase in life expectancy at birth of three months during the period.[100]

Other scholars who examined the increased well-being resulting from PDUFA I and PDUFA II concluded that the speedier approval saved the equivalent of 140,000 to 310,000 life-years, a much higher figure than Gieringer's estimate from the pre-PDUFA period. They concluded that drugs approved under PDUFA I and II but later withdrawn cost *at most* 56,000 life-years. They emphasize that this is very much an upper bound to the estimate, assuming that no patients benefited from one of the withdrawn drugs before it was withdrawn, and that all withdrawals were entirely due to the speedier approval under PDUFA I and II—that is, that the drugs would never have been approved without PDUFA.[101]

PDUFA's effects are clearly positive. Unfortunately, PDUFA's success at eliminating drug lag gives false hope that the FDA's problems are solved.

A FASTER FEDERAL REGULATORY MONOPOLY IS NOT ENOUGH

Despite speedier approval, the FDA still harms patients by needlessly delaying their legal access to new medicines. Shrinking the average from three years to slightly more than one year is certainly beneficial, but the evidence indicates that even one year of lost treatment costs lives. Consider the midpoint of the earlier estimate: that the speedier approval saved about 225,000 life-years versus costing about 25,000 life-years, for a net improvement of about 200,000 life-years. This implies that even a one-year delay costs about 200,000 patients their lives, because of delayed legal access to new medicines.

Nor are academic papers the only source of information about the harm done by the federal government's automatic ban on new medicines. A number of patient-advocacy groups are active in seeking more freedom from the FDA. The Abigail Alliance for Better Access to Experimental Drugs, a charity founded in 2001, leads a number of similar groups in lobbying for legal and regulatory changes to the status quo, among other objectives. Challenging the FDA's "non-responsive" bureaucracy and "antiquated scientific approval process," the Abigail Alliance comprises families who have lost loved ones they believe would have had a good chance of survival if the government had not prohibited them from using medicines before the FDA approved them. The Abigail Alliance notes that every drug for which it advocated use in the first six years of its existence was subsequently approved by the FDA. Frank Burroughs, founder of the Abigail Alliance, and father of Abigail, who died of cancer at age 21, describes the FDA as a "stagnant agency existing in a constant state of institutional worry."[102]

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Surveys of randomly sampled specialists unaffiliated with the FDA, but who treat patients affected by the FDA's intervention, demonstrate a more favorable judgment of the FDA's post-PDUFA's standards but would like to see even quicker approvals. Most recently, a survey of 175 orthopedic surgeons, conducted in December 2006 and January 2007, revealed that 76 percent of respondents believed the FDA approval process was too slow; 60 percent believed that it hindered their use of new therapies; 70 percent favored changing laws to allow physicians to prescribe unapproved drugs if they carried an appropriate warning; and 80 percent favored making Vioxx™ available again.[103]

In a 2002 survey of 160 oncologists, 48 percent said that the FDA had improved its approval of new drugs and devices. Nevertheless, 61 percent agreed totally with the statement that the FDA was too slow to approve new drugs and devices, whereas only 37 percent disagreed totally. The numbers were almost exactly the same (60 percent versus 39 percent) for the statement that the FDA forced patients to go without potentially beneficial therapies. Further, the oncologists thought that only 24 percent of the general public understood the human cost of the FDA's processes, and 70 percent did not understand it at all.[104]

The unanswered question is whether a government monopoly regulator can reform itself.

A previous survey of 200 emergency-room physicians in the United States found similar results. A full 64 percent of those surveyed agreed totally that the FDA was too slow to approve new drugs and devices, and 73 percent agreed that the general public did not understand the costs.[105] A survey of 202 neurologists and neurosurgeons found that 67 percent of these specialists believed that the FDA took too long to approve new drugs, and 58 percent believed that this delay costs lives. Of these specialists, 73 percent believed that the public had little or no understanding of this problem, and 57 percent believed that FDA restrictions harmed their ability to provide the best possible medical care at least some of the time. Further, 70 percent opposed FDA restrictions on information about "off-label" use of medicines.[106]

Many physicians and patients are content to use prescription drugs for purposes other than those authorized by the FDA. Once the government lifts its ban on a new drug, physicians often prescribe it for conditions other than those for which it was approved, although government does not allow companies to communicate the benefits of such uses. This off-label prescribing is very common; most pediatric patients and many AIDS and cancer patients receive prescriptions for drugs the FDA approved for other conditions.[107]

MEDLINE, an index of medical literature, has a drug database on the Internet that lists off-label uses for prescription medicines. Through off-label prescribing, physicians and patients inform us that they consider themselves capable of judging when to use a given medicine, whether or not the government has approved it for a particular condition. A study of 100 of the 500 most frequently prescribed drugs, plus 60 other randomly selected drugs, found that one-fifth of the prescriptions in 2001 were for off-label uses.[108] Perhaps the most absurd example of the label cult occurred in 2005, when the FDA approved new labeling for Iressa™, a drug for lung cancer, which permitted its use by patients already taking it, but not for future patients who had not undergone a clinical trial.[109] Furthermore, a 2009 survey of health plans concluded that three-quarters of them reimburse off-label uses of prescription drugs.[110]

Remarkably, despite the clear benefit that doctors and patients derive from using prescription drugs off-label, the FDA enforces regulations preventing manufacturers from communicating off-label benefits. From 2003 through 2007 the agency issued 42 letters to drug companies requesting that they stop marketing drugs for off-label uses—an average of more than eight letters per year. However, other complainants also referred drug companies to the Department of Justice, resulting in 11 settlements during that period.[111]

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In 2009, Pfizer, Inc., paid the largest fine ever levied against a drug maker for encouraging off-label prescribing: more than $1 billion for the promotion of the painkiller Bextra™ from 2002 through 2005, when it was withdrawn due to safety concerns.[112] On the other hand, Allergan, Inc., sued the FDA last year, seeking a declaratory judgment that the FDA's regulations against off-label promotion constitute a violation of free speech, and are contrary to both regulatory and legal precedent.[113]

This introduces a subject that has come under increasing scrutiny: the FDA's role in monitoring the use of a medicine after the agency has approved the medicine for use. The original concept enshrined in the Food, Drug, and Cosmetic Act has a bias that PDUFA has not succeeded in overcoming. Imposing a binary approval process—that is, simply to approve or not to approve—causes interested parties to invest too much in gaining initial approval and not enough in meeting the challenge of incorporating new information about a therapy's effectiveness and side effects after it is in use. Indeed, there is a legitimate concern that PDUFA has biased the FDA's commitment of resources toward new drug reviews to the detriment of post-approval surveillance.

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In 1993 the FDA allocated 53 percent of funds to new drug review; that figure had gone up to 70 percent by 2003.[114] This share has recently receded: Congress' FY 2010 appropriation for the FDA included $880 million for regulating human (non-veterinary) drugs. A full $447 million was for new drug approvals (of which two thirds, $298 million, was covered by user fees), but only $149 million was for post-market safety oversight (of which slightly less than half, $72 million, was covered by user fees).[115]

PDUFA I (1992) directly linked revenue from user fees with the number of new drugs approved by the FDA. Because this biased the FDA's incentives, PDUFA II (1997) targeted a lump sum to be raised by user fees, independent of the number of new medicines approved. Nevertheless, the law prevented the FDA from spending user fees on anything other than approving new drugs, which resulted in reduced post-marketing surveillance.[116] The FDA's Center for Drug Evaluation and Research (CDER) does run its own post-marketing surveillance. Usually, manufacturers must submit adverse-event reports every 15 days for three years, and then annually. As well, patients, doctors, pharmacists, and other health care professionals can voluntarily submit adverse-event reports directly via a system called MedWatch. This results in more than 400,000 reports a year.[117]

More robust adverse-event reporting, however, comes from the private sector, with which the CDER contracts. Four groups—the HMO Research Network, Vanderbilt University, the Kaiser Foundation Research Institute, and Ingenix, Inc. (a commercial vendor of data)—generate such information. Combined, these four outfits have data on 23.5 million people.[118] Remarkably, CDER does *not* have seamless access to the Veterans Administration (VA) database, which has automated databases for millions of veterans in more than 1,300 care sites.[119]

Despite all these public and private resources, we do not really know how many adverse drug reactions (ADRs) occur. A 2001 analysis of 20 peer-reviewed studies plus one meta-analysis found a range of prevalence of fatal adverse drug events from 0 to 2.3 percent. The article concluded that there is no good

estimate of the systemic number of fatal adverse events in the United States. Perhaps unsurprisingly, given the difficulty of gathering data on ambulatory patients, 14 of the studies were conducted on in-patients.[120] Considering that the total cost of developing a new medicine is $1.3 billion, this is a remarkable systemic failure.[121]

Certainly, identification of adverse events after a drug is approved and is being used in general practice is fraught with confounding factors, many unobserved. However, the FDA is currently called upon to issue warnings or demand that a drug be withdrawn on such grounds anyway.[122] When the FDA issues a black-box warning about a medicine's side effects, it can cause the use of the drug to drop below what doctors think is optimal. This happened with the antidepressants Zoloft™ and Prozac™ when the FDA warned against their use in children.[123]

A survey of 175 orthopedic surgeons, conducted in December 2006 and January 2007, revealed that 76 percent of respondents believed the FDA approval process was too slow.

Perhaps not surprisingly, given the perverse incentives described earlier, the climate of public opinion seems to lean in favor of giving this federal monopoly even more power. Most health care elites take a similar position. After all, the FDA definitely *wants* to speed up its approval processes in a scientifically responsible way. Indeed, to achieve this objective, in 2005 the FDA funded an independent body, the Critical Path Institute, to develop its own Critical Path Initiative to make itself more effective.[124] The unanswered question is whether a government monopoly regulator can reform itself.

In 2006, the FDA's centennial, the government commissioned the Institute of Medicine (IOM), an independent, government-funded body, to establish a Committee on the Assessment of the U.S. Drug Safety System. The committee published a report proposing 25 recommendations, all of which would increase the costly burden of regulation, and none of which would increase Americans' freedom to use medicines that they and their doctors choose.[125] This report has been frequently cited by the media and proponents of reform in calls for *more* regulatory oversight, despite its portrayal of a classically inefficient monopoly.

Indeed, the committee goes so far as to describe the CDER as suffering from "organizational dysfunction."[126] Its report concludes that the CDER does not even have a standard means of measuring risk and benefit. For both pre-marketing and post-marketing review, risk-benefit analysis appears to be "ad hoc, informal, and qualitative."[127] "Differences of opinion among reviewers may surface at various points during the review process or in the postmarket period. . . . Reviewers rarely have all the information they would like to have to make the required scientific determinations."[128]

The committee identified cultural tension between the two groups within CDER responsible for the different tasks of pre-marketing approval and post-marketing surveillance, and noted that PDUFA was designed to expedite approval, not to foster post-market review. The committee concluded that the FDA's legal authority to compel compliance from interested parties after a new medicine is approved for use is uncertain.[129]

One might be forgiven for asking how much regulation these scholars want. After all, the committee recognizes that an adverse event that occurs in less than one in a thousand patients, no matter how serious, is unlikely to be detected. On the other hand, clinical trials conducted in order to gain the

FDA's approval can neither determine the long-term effects of using a drug nor anticipate the effects on the various different types of patients who will actually use a drug once it is available to the general population. This is because clinical trials often avoid enrolling subjects who have diseases other than the one in question or who are taking other medications.[130]

On the other hand, patients react quickly to privately generated information in the absence of a government ban on a therapy. After the release of a study in 2002 that demonstrated that hormone replacement therapy (HRT) appeared to do more harm than good for most women (by increasing the risks of breast cancer, stroke, and other ailments), sales of Prempro™, the leading therapy, collapsed from $2 billion in 2001 to $500 million in 2002.[131]

Despite PDUFA, many argue that the FDA needs more resources to do its job. Even those subject to the FDA's monopoly power make this argument. The past chairman of PhRMA, the trade association for research-based pharmaceutical companies, asserted as recently as 2009 that the FDA was "understaffed and under-funded."[132]

It is exceedingly difficult to arrive at such a conclusion. PDUFA succeeded in enlarging the FDA's bureaucracy significantly. The number of personnel conducting drug reviews doubled, from 1,300 to 2,600, between 1992 and 2007. User fees, which originally made up 30 percent of the FDA's budget, now account for more than half.[133] The CDER had a budget of about $500 million for 2007, of which about $240 million was from user fees.[134] User fees first accounted for more of the CDER's budget than appropriations did in 2004.[135] Similarly, the number of staff for new drug review supported by user fees (1,320) was higher than the number supported by appropriations (1,287) for the first time in 2004.[136]

The FDA's user fees, furthermore, are significantly higher than those of comparable regulators in other countries. As early as 2001, the FDA charged manufacturers approximately $250,000 for reviewing each new medicine, whereas the European regulatory agencies charged the equivalent of between $90,000 and $100,000.[137] Unfortunately, the additional cost has not resulted in increased productivity.

Table 3 shows the number of personnel (full-time equivalent) employed in approving new drugs at various national regulatory agencies in 2000. The FDA employed far more people than any of the other national regulators to deal with each New Drug Application (NDA).

Table 3: Staff for Drug Approval and Drug Applications in Five Countries

	New Drug Approval Staff, Full-Time Equivalent, 2000	Average Annual No. of Applications for New Active Substances, 1999 through 2001	Full-Time Equivalent Staff per Application
Canada	159	26	6
Australia	76	30	3
Sweden	46	30	2
United Kingdom	60	24	3
United States	1,610	28	57

Source: Rawson 2002, p. 75; Rawson 2003, p. 1235; author's calculations (figures rounded to whole numbers)[138]

Table 4 shows an index of productivity of pharmaceutical regulation as a function of the full-time equivalent staff per application and the median time to approval in the five countries. Sweden performs best, scoring 100. Recall that these national regulators are generally reviewing the same medicines. The first thing that jumps out is that the United States performs extremely poorly, despite its short time to approval. The FDA employs too many people and costs too much, and it is only getting worse. The FDA's actual spending on regulating human drugs in 2009 was $802 million; $880 was appropriated in 2010, and the president's 2011 budget demands one billion dollars.[139] This amounts to an increase of 20 percent over two years. After getting more money in 2008, the FDA went on a "hiring surge," taking on 2,500 more employees in 2008 and 2009. Indeed, the agency *exceeded* its hiring targets last year.[140]

Table 4: Productivity of New Drug Approvals for Five Countries, 1999–2001

	Full-Time Equivalent (FTE) Staff per Application	Median Time to Approval (Days)	Productivity Index (FTE Staff Relative to Median Time to Approval)
Canada	6	645	38
Australia	3	551	77
Sweden	2	431	100
United Kingdom	3	479	68
United States	57	371	2

Source: Rawson 2002, p. 75; Rawson 2003, p. 1235; author's calculations (figures rounded to whole numbers)[141]

For FY 2010, each NDA requiring clinical data costs $1,405,500 in user fees. For an application that does not require data, or a supplemental application that requires data, the fee will be $702,750. (These are generally generic drugs or drugs with minor modifications, such as dosage.) There are also recurring annual fees for each pharmaceutical establishment ($457,200) and each product that has been already approved ($79,720).[142]

This state of affairs, whereby even PDUFA's limited success is twisted into an argument for an even more comprehensive federal monopoly of pharmaceutical regulation, led to the FDA Amendments Act of 2007 (FDAAA), which re-authorized PDUFA and significantly increased the FDA's regulatory power. Like previous amendments to the Food, Drug, and Cosmetic Act, the FDAAA was passed in a heated environment, in which politicians and the public had been whipped up by negative reports on a small number of medicines, such as Vioxx™ and a certain class (SSRI) of antidepressants, as well as by coverage of the IOM committee's unflattering report. This happened even though at least one scholarly reviewer of the committee's work criticized it for selective consideration of evidence.[143]

Although FDAAA increased the agency's responsibilities for post-marketing surveillance and granted it authority to compel drug makers to execute so-called "risk management plans," a 2009 audit by the Government Accountability Office concluded that "additional actions are needed" for the FDA to execute its responsibilities. Among the problems identified by the GAO are the lack of a method of resolving scientific disputes, lack of a "time frame" for allocating authority between offices within the FDA, and difficulty filling vacancies.[144]

As noted previously, PDUFA IV (2007) significantly increased user fees, and it also gave the agency greater power to require post-marketing studies, as well as to enforce drugmakers' publishing details of their clinical trials on an expanded government-run, open-access database. Nothing in PDUFA IV requires the FDA to become more efficient versus its international competitors. On the contrary, it introduces at least two more negative consequences of the agency's power. First, by giving the FDA explicit authority over post-approval drug use, it invites yet another government agency to control physicians' behavior. Second, it allows critics to cherry-pick "undigested" clinical trial data from the open-access database in order to scandalize the public with research taken selectively and out of context.[145]

Finally, by extending the federal regulatory monopoly even more into the area of post-approval surveillance, while not reforming pre-approval regulatory requirements, PDUFA IV continues to ignore the needs of patients with life-threatening illnesses. Advocates argue that placebo trials are not appropriate for the approval of drugs for life-threatening diseases for which there are no other options. Indeed, they argue that it is unethical for the FDA to demand that half of the subjects in a clinical trial be assigned to the placebo group if certain death is the outcome. Rather, a trial that gives all subjects the investigational drug can be analyzed with statistical techniques that determine safety and effectiveness versus historical data.[146]

No matter now much money government allocates to it, a monolithic federal regulatory monopoly can never serve American patients' diverse needs for new, innovative prescription drugs.

THE FDA CHARGED MANUFACTURERS APPROXIMATELY $250,000 FOR REVIEWING EACH NEW MEDICINE, WHEREAS THE EUROPEAN REGULATORY AGENCIES CHARGED THE EQUIVALENT OF BETWEEN $90,000 AND $100,000.

RECENT PERFORMANCE:
U.S. versus European Regulators

Because the data comparing the performance of U.S. and European regulatory bureaucracies discussed earlier is from no later than 2005, this edition of *Leviathan's Drug Problem* reports new information on the comparative performance of the FDA and its European counterpart, the European Medicines Agency (EMA).

After getting more money in 2008, the FDA went on a "hiring surge," taking on 2,500 more employees in 2008 and 2009. Indeed, the agency exceeded its hiring targets last year.

We identified 39 new drugs or biologicals that had been approved by either the FDA or the EMA during the 12 months from May 2008 through April 2009 (table 5). These drugs were either New Medical Entities (NMEs) or combinations, or new biologicals. Therefore, the list excludes generic versions of previously approved medicines or licenses that simply authorize new dosages or a change of manufacturer of a previously licensed medicine.

Table 5: New Medicines Approved by U.S. Food and Drug Administration or European Medicines Agency: 5/1/2008 through 4/30/2009		
Approved by FDA or EMA?	Medicine's Proprietary Name	Days Delayed (Negative number of days indicates that the FDA approved first; positive that the EMA approved first; N/A if only one regulator approved)
EMA only	Thymanax / Valdoxan	N/A
EMA only	Conbriza	N/A
EMA only	Ceplene	N/A
EMA only	Stedesa	N/A
EMA only	Firazyr	N/A
EMA only	Tykerb	N/A
EMA only	Fablyn	N/A
EMA only	Mepact	N/A
EMA only	Xarelto	N/A
EMA only	Bridion	N/A
EMA only	Cordaptive	N/A
FDA only	Entereg	N/A
FDA only	Coartem	N/A
FDA only	Ulesfia	N/A
FDA only	Cleviprex	N/A
FDA only	Durezol	N/A
FDA only	Promacta	N/A
FDA only	Afinitor	N/A
FDA only	Lusedra	N/A
FDA only	Eovist	N/A
FDA only	Adre View	N/A
FDA only	Savella	N/A
FDA only	Mozobil	N/A
FDA only	Rapaflo	N/A
FDA only	Tapentadol	N/A
FDA only	Xenazine	N/A
FDA & EMA	Vidaza	(1,673)
FDA & EMA	Doribax	(287)
FDA & EMA	Intelence	(223)
FDA & EMA	Effient	135
FDA & EMA	Ranexa	(894)
FDA & EMA	Kuvan	(355)
FDA & EMA	Uloric	298
FDA & EMA	Toviaz	560
FDA & EMA	Vasovist	1,176
FDA & EMA	Banzel	668
FDA & EMA	Firmagon	(55)
FDA & EMA	Vimpat	60
FDA & EMA	Relistor	(69)
Source: Author's analysis of data from the FDA and EMA.		

Of these 39 new medicines, 15 were approved only by the FDA, 11 were approved only by the EMA, and 13 were approved by both regulators. In only three cases did the FDA and EMA both approve the medicine in question within the 12 months reviewed. In five of the 13 cases where the FDA and EMA both approved the medicine within the period, the EMA was the first to approve, and it issued those approvals 552 days faster than the FDA, on average. Even if we include all 13 medicines approved by both the FDA and the EMA, the EMA approved them 97 days faster, on average.

Furthermore, of the medicines which the EMA alone had approved, the FDA was processing the application in all cases during the 12 months considered. It's not that the manufacturers had simply decided not to apply for U.S. approval! If the U.S. government had allowed American patients to use new medicines that were approved by the EMA, but not yet the FDA, American patients would have had faster access to 17 new medicines, out of the entire set of 39. Clearly, Congress' grant of a regulatory monopoly to the FDA is creating a significant obstacle to Americans' timely access to new medicines.

OPTIONS FOR REFORM:
Increasing Choice through International Competition

Allowing Americans to use a new drug as soon as the EMA licenses it is a reasonable reform that would give Americans more timely access to new medicines. In this case, the FDA would become more productive because it would be competing for user fees with similar regulators in other countries. As soon as the EMA approved a new medicine Americans would have the right to use it.

The FDA, however, would retain the right to compel a manufacturer to add a warning label to a new medicine stating that it *would have banned* the drug if it still had that power. The FDA could also distribute its "would have banned" warnings to professional publications such as *JAMA: Journal of the American Medical Association* and through other communications to health professionals, such as the "Dear Health Professional" letters currently sent out for adverse drug reactions that arise after a drug is distributed. The FDA could also communicate its preferences to the general public via its website, publications, or advertisements. If the FDA chose, it could then approve the medicine according to its own time frame, but funded only by taxes, not user fees. If the manufacturer thought it valuable to have the FDA remove its warning label, it could pay a user fee to have the department review and certify the drug, as currently takes place.

Each physician could choose whether to prescribe drugs not actively approved by the FDA. State health departments, state medical licensing boards, and medical associations could even produce lists of doctors who do or do not prescribe medicines not certified by the FDA. That would facilitate patients' ability to inform themselves about the risks of the drugs available to them through different practitioners.

> No matter now much money government allocates to it, a monolithic federal regulatory monopoly can never serve American patients' diverse needs for new, innovative prescription drugs.

This option could be legislated for a period of, for example, five years. During that period, prescribing information would be captured by groups such as IMS Health, Inc., Express Scripts, and other data vendors. This information would inform Congress and the people about the degree to which patients valued the FDA's input into their decisions about the medicines they use, versus the input of other national regulators such as those in the EU. If patients really think it is important for our government to stop us from using new medicines, few will ignore "would have banned" labels and we will be more confident that the FDA provides a valuable function. Congress can then revisit the reform. If many patients use medicines approved by a foreign regulator, then we can move to even less regulation, as described shortly.

There are a couple of caveats concerning this deregulation. First, patents are intellectual property rights created by national governments. There are medicines protected by patent in the United States that are not patented in other countries. Therefore, the U.S. government should not allow patients to steal the intellectual property of drugmakers whose medicines are still patented in the United States by approving their use of generic medicines certified by regulators in countries where the drug is not patented.

> The federal government's regulatory monopoly unduly restricts Americans' ability to access innovative prescription drugs.

Second, the government, as part of its role in policing misbranded or adulterated medicines, would still need to keep a watch on our borders to ensure that counterfeit drugs, or those that have been illegally misappropriated from manufacturers' distribution systems, are not allowed to enter the country.[147]

Within the limits of these two caveats, Americans' health and welfare will increase if Congress amends the Food, Drug, and Cosmetic Act to require the FDA to approve an NDA when the drugmaker notifies the FDA that a comparable foreign jurisdiction, such as one in the EU, has lifted its ban on the new medicine. The amendment would allow the FDA to compel the drugmaker to put a warning label on the drug, and to communicate with health professionals and the general public that it did not actively approve the drug, as described previously.

The amendment would further require the FDA to make an annual report concerning the reciprocal NDA approvals issued under the amendment, as well as the application and removal of warning labels by the FDA and the number of prescriptions written as a result of these actions.

After a period of five years, Congress would review how Americans responded to the amendment and introduce further regulatory reform based on that information. This might include adding private certifying bodies to the list of those whose approval is acceptable for the interstate traffic of prescription drugs.

The reform just described is radically different from the status quo. However, there is already a legislative option that gives more choice, at least to seriously ill patients. This year, Representative Diane Watson introduced the Compassionate Access Act, which defines Compassionate Investigational Access. This bill would authorize the Secretary of Health and Human Services to permit an unapproved drug to be made available under certain conditions. The drug must have had Phase 1 clinical trials and be ready for Phase 2 trials, and the sponsor must be pursuing FDA approval in good faith. Patients must be seriously ill, have exhausted other treatments, and be ineligible for a clinical trial for various reasons.

Patients must sign consent forms, and the drug must have a special label, which would limit the drugmaker's tort liability. The bill would also establish an Accelerated Approval Advisory Committee, to include representatives of patients and drugmakers and establish a five-year pilot project for Medicare to cover accelerated compassionate use for its beneficiaries, after which a report on the effects of the program would be presented in Congress. The bill would also encourage the FDA to use measures other than placebo trials to determine the safety and efficacy of such new drugs.[148] All of these reforms are commendable.

Randomized clinical trial of an investigational new drug versus a placebo has long been accepted as the gold standard of research. The prospect of tampering with this standard concerns many people. Of

course, "rushing" a new drug to the market increases the risk that the sponsor will not be able to conduct such a large-scale, randomized clinical trial. However, an era in which medicine is seeking to become more personalized invites more innovative trials. A former FDA deputy commissioner has suggested a number of ways to mitigate the risk.[149]

One would be for the FDA to communicate to the research community the surrogate endpoints that it would like to see qualified for speedier evaluation. It might also incorporate "adaptive" approaches, such as over-enrolling patients in trials, based on characteristics that suggest they would be more likely to have a favorable response (such as expressing a certain enzyme that stimulates cancer tumors). Researchers could also mimic the effects of a placebo by using historical matched controls in trials for diseases where the natural history is well understood. This would allow more patients access to experimental treatments without the risk that they would get randomized to the placebo group.

Through this reform, the FDA would evolve from a certifier of products to a certifier of certifiers.

If successful, the two reforms described in this paper would give the American people confidence that they could free themselves even more from the government's regulatory burden. Ultimately, this would include moving toward private certification of all new medicines. In this case, manufacturers would have the sole responsibility of convincing physicians and patients that they should use any new drug. Physicians and patients would likely demand that manufacturers submit their new drugs to private bodies, likely non-profit, to certify their risks and benefits. As suggested by the greater relative productivity of European pharmaceutical regulators, who operate in a quasi-competitive environment with other members of the EU, this would also ensure greater productivity of those certifying the results of the testing. This option, we should note, derives from actual practice in other areas of risky human endeavor.

One example is Underwriters Laboratories (UL), founded in 1894 as an independent, non-profit organization. UL has certified products for much longer than the FDA. It certifies tens of thousands of different products related to areas such as electrical safety, fire suppression, and safety of liquid gas. Indeed, its many thousands of clients include government agencies. No law requires certification by UL, but governments accept UL certification for many areas in which they regulate standards.[150]

Another example is the Snell Memorial Foundation (SMF), founded in 1957 by friends of William "Pete" Snell, a racecar driver who died of head injuries sustained when his helmet failed to protect him. The SMF was motivated by the goal of improving the effectiveness of helmets, and it now sets standards for all types. Many people engaged in activities for which helmets are an important safety feature, such as mountain biking, value the SMF certification, and this motivates manufacturers to submit their helmets for testing, at their own cost, although there is no legal requirement to do so. The SMF limits itself to the business of researching and testing the effectiveness of helmets. It does not advocate for mandatory helmet laws and has never lobbied on any pertinent legislation. According to the SMF, its standards surpass those of the U.S. Department of Transportation and the U.S. Consumer Products Safety Commission.[151]

This method of certification has two advantages. First, because private certifiers operate in a competitive environment, they would be more productive than the FDA, a government monopoly. Second, private certifiers would likely recognize a range of standards for safety, rather than one-size-fits-all.[152] This

means that Americans who prefer to accept more risk with their medicines would be able to act on earlier, less complete information about the effects of a new medicine. On the other hand, Americans who are more risk-averse could wait for a higher standard of certification that would result from more expensive and thorough testing. The U.S. government would not compel any patient to accept another's standard of safety.

Through this reform, the FDA would evolve from a certifier of products to a certifier of certifiers. In this respect, it would largely return to its earlier role: ensuring that products are not misbranded or adulterated.[153] Given that every comparable country has a national pharmaceutical regulator with some degree of monopoly power (although there is some intra-EU competition), it is likely too much to expect the United States to act alone in private certification.

Finally, the need for reform of American drug-approval policy is beyond dispute, but all reform should begin with recognition of key realities, supported by history. From aspirin and penicillin, through the Salk vaccine, all the way to Lipitor® and other modern medicines, new drugs have helped Americans and people around the world to live longer and healthier lives. These new drugs are the products of pharmaceutical innovators, not the Food and Drug Administration or any other government agency. The federal government's regulatory monopoly unduly restricts Americans' ability to access innovative prescription drugs. Legislators have available a range of options to break up that regulatory monopoly. All are worthy of serious consideration, and many will prove worthy of eventual adoption. The evidence, meanwhile, is clear that merely spending more money on the FDA is highly unlikely to result in better outcomes for patients.

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ABOUT THE AUTHOR

John R. Graham is director of Health Care Studies at the Pacific Research Institute. He is the author of a number of studies, including ***Taxing Health Insurance: How Much Do States Earn?*** and ***Medicare Advantage or Medicare Monopoly?*** Graham is also the author of the ***U.S. Index of Health Ownership***, the only project to rank all 50 states' health laws and regulations according to free-market principles, and the editor of the book, *What States Can Do to Reform Health Care: A Free Market Primer*.

Graham writes the monthly ***Health Policy Prescriptions*** series, which addresses national health care reform, and contributes to PRI's ***Capital Ideas*** series of short articles on public policy in California. He has written articles about health policy for periodicals including the *Wall Street Journal* and the *Washington Post,* and writes frequently for blogs including *National Review Online* and *John Goodman's Health Policy Blog*. His Twitter handle is johnrgraham.

Graham has also worked as a management consultant and investment banker in Canada and Europe and is a Canadian Army veteran. He received his M.B.A. from the London Business School (England) and his B.A. (with Honors) in Economics and Commerce from the Royal Military College of Canada.

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