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PERSPECTIVES

ESSAY

Governmental influences on drug development: striking a better balance

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Abstract | There is currently considerable debate in many countries over the effects of public policy — in particular, governmental regulation — on the development of innovative pharmaceuticals. Regulators must balance patients' access to therapies with ensuring the safety of drugs. The consequences of poor decisions can be dire: if access is promoted at the expense of safety, a dangerous product can cause incalculable harm; conversely, if safety is over-emphasized at the expense of access, patients can suffer from the absence of life-saving and life-enhancing medications. Using the United States as an example, we discuss the influence of governmental bodies such as the US Food and Drug Administration (FDA), as well as recent legislative initiatives, on pharmaceutical innovation. We argue for a balanced approach to governmental interventions.

Governmental influences on drug development can be positive. In the United States, the research funded by the federal government (primarily the National Institutes of Health but also the National Science Foundation and several others) that attempts to better understand fundamental processes and to establish 'proof of concept' often provides the scientific substrate that is essential to downstream product development. For example, recombinant DNA technology, which is now ubiquitous in basic research and drug discovery, was the product of synergistic advances in several areas of government-funded research, including enzymology, microbial genetics and physiology, and separation technologies. The National Institutes of Health also carries out some clinical trials, and even occasionally undertakes early research and development on a drug (examples include paclitaxel, the anticancer drug, and erythropoietin, which stimulates the bone marrow to produce red blood cells and is used to treat certain anaemias). And as a repository of safety data on all drugs, the US Food and Drug Administration (FDA) possesses information that no other organization commands, which it can make available to health practitioners and the public. In addition, recent research-orientated initiatives from the FDA, such as the Critical Path Initiative, have the potential to help to address industry-wide issues, such as the need for better animal models of human disease and for biomarkers of drug efficacy and toxicity.

However, by imposing policies that can unduly hamper innovation, governmental actions can exert a significantly negative influence on drug development. Policies that will affect drug pricing and drug regulation are currently the subject of considerable debate in the United States and elsewhere, and there is growing momentum for governmental actions to address the perceived problems in these areas. On the one hand, as a result of concerns about the rapid growth in health-care spending, efforts to contain the prices of new drugs (which in many countries are set by the government) are attracting increasing attention in the United States, which has long resisted such controls. On the other hand, high-profile problems (or alleged problems) of drug safety have led to calls to increase the stringency of drug regulation, which would increase the already astronomical costs to drug developers to bring a drug to market; and that would, in turn, raise the prices that would need to be charged to payers for the developer merely to recoup the investment made in drug discovery and development.

Both aspects of public policy are the focus of bills that are currently under discussion by the US Congress (BOX 1). As discussed below, some previous interventions of the US Congress have impeded new drug discovery and development, and have created uncertainty and confusion — a situation that is anathema to corporate planning of this lengthy and risky process. With this in mind, we discuss the role of governmental influences in drug discovery and development, highlight the factors that should be considered in order to avoid governmental interventions that negatively affect pharmaceutical innovation, and suggest how reforms could help to improve the status quo.

Price controls

There is considerable evidence that drugs often improve the span and quality of life in a remarkably cost-effective way. This is of crucial significance not only to the individual patient but to society as a whole: the responsible use of drug therapies lowers the total cost of health care. For example, a study by three leading health economists for the National Bureau of Economic Research in the United States found that the overall cost of therapy for heart attacks and depression — both of which are commonly treated with drugs — actually declined by an average of 1% each year from 1984 to 1991 (REF. 1). Similarly, the costs of treatment per episode of major depression fell by 25% from 1991 to 1995 (REF. 2), and studies of the impacts of a thrombolytic drug in stroke patients[3] and a new drug for migraine headaches[4] show that these treatments are highly cost-effective. Furthermore, new drugs typically confer an advantage over older ones in reducing mortality. According to a study of patients who took drugs at any time between January and June 2000, those who took newer medications were less likely to die by the

end of 2002. The estimated mortality rates were directly related to the time that had elapsed since the approval of the drugs. For pre-1970 drugs, the estimated mortality rate was 4.4%, whereas the mortality rates for drugs approved during the 1970s, 1980s and 1990s were 3.6%, 3.0% and 2.5%, in corresponding order[5].

Although such studies provide evidence for the health benefits and cost-effectiveness of the introduction of new drug therapies, there are now increasing efforts to control the prices of drugs in the United States, which, unlike Japan and Europe, for the most part has eschewed such controls. It is therefore notable that some researchers have argued that even in the United States, the impacts of price control efforts have been significant nevertheless. For example, a group at the Center for Healthcare and Insurance Studies at the University of Connecticut reported that prices fall as the government's share of spending on drugs increases, and that this exerts a negative effect on innovation and, ultimately, on public health[6]. They studied US data from 1960 to 2001 and found that, owing to the influence of laws intended to curb drug prices under government-run programmes, "from 1992 to 2001 a 10 percent increase in the growth of government's share of total spending on pharmaceuticals was associated with a 6.7 percent annual reduction in the growth of pharmaceutical prices."[6] When the government increases its share of spending, argue these researchers, pharmaceutical companies considering an investment in the development of new drugs can look forward to lower revenues, and this reduces their incentive to innovate.

Using regression analysis, they concluded that in the absence of any governmental influence exerted on drug prices, prices would have been about 35% higher, and that the "government-induced loss of capitalized pharmaceutical R&D expenditures was $188 billion (in 2000 dollars) from 1960 to 2001". Applying econometric models on the productivity of pharmaceutical R&D in the United States over the same period, they translated this foregone R&D into 140 million human life-years lost as the result of increased pain and suffering and lives shortened by the absence of new medicines. This was equivalent to more than half a year of life lost per person in the United States at the time.

Notwithstanding such findings, the Democrats who now control Congress want to change the Medicare drug benefit to require government officials to negotiate drug prices with the pharmaceutical companies — which amounts to price controls. (Under the current programme, competing insurance companies individually negotiate the deals and offer coverage to the retired and disabled.) Could anyone think that the government using its monopolistic muscle to force drug prices to sub-market levels will stimulate drug companies to develop more life-saving drugs?

The precedent of the Veterans Administration health-care system suggests that another likely outcome of such compulsory negotiations will be that the government will decide not to cover certain drugs under Medicare at all. Only 19% of drugs approved by the FDA since 2000 are listed on the Veterans Administration formulary, and less than 40% of drugs approved in the 1990s are listed.

Box 1 | **Upcoming congressional bills**

Enzi–Kennedy Bill, Enhancing Drug Safety and Innovation Act of 2007, S. 484:

- A bill proposed to the US Senate
- Provides additional resources for the US Food and Drug Administration's (FDA) drug safety office and makes it organizationally independent of the FDA's drug-approval function
- Enables the FDA to require clinical trials
- Requires drug approvals to be accompanied by post-marketing risk evaluation and mitigation strategies (REMS) that are intended to help companies and regulators to assess post-marketing adverse-event reports and to communicate risk information to the public; REMS could include mandatory post-marketing safety studies, restrictions on which providers can prescribe or dispense a drug and limitations on direct-to-consumer advertising
- REMS may require drug companies to develop medication guidelines for distribution when a drug is dispensed, patient package inserts, and plans for disseminating risk information to health-care providers
- Under REMS, pharmaceutical companies may also be required to conduct post-marketing (Phase IV) trials
- Creates an institute that would identify new tools for biomedical research
- Requires all clinical trials to be registered and their results stored in a public database

Waxman–Markey Bill, Enhancing Drug Safety and Innovation Act of 2007, H.R. 1561:

- The companion bill to the Senate's Enzi–Kennedy Bill (S. 484), with similar provisions, proposed to the US House of Representatives

Dodd–Grassley Bill, Fair Access to Clinical Trials Act, S. 467:

- A bill proposed to the US Senate
- Gives the FDA more power to require manufacturers to conduct post-marketing surveillance and other measures that are related to the safety of newly approved drugs
- Creates a new organizational entity within the FDA to oversee post-approval drug safety that would report directly to the FDA commissioner

The FDA's influence

Although there are other governmental influences on pharmaceutical development in the United States, regulation by the FDA is certainly the most potent and has long been a major focus of attention, analysis and criticism. Over the past several decades, the pendulum has swung over what ails pharmaceutical regulation. Thirty years ago, the concerns were primarily about 'drug lag' — slow reviews and approvals by the FDA that put Americans at a disadvantage to consumers in other countries; but, in recent years, concern has shifted primarily to what might be called 'drug leap' — allegations of hurried approvals, insufficient attention paid to drug safety, and too close a relationship between regulators and industry. Several highly publicized events have heightened public concern about drug safety during the past few years: inadequate warnings on the labels of anti-depressants, the discovery of previously unknown adverse reactions to non-steroidal anti-inflammatory drugs (NSAIDS) and the multiple sclerosis drug natalizumab (Tysabri; Biogen-Idec), and the dramatic decompensation of volunteers almost immediately after receiving the first dose of a drug (TGN1412) in a Phase I trial in England.

However, contrary to these perceptions, drug regulation in the United States in recent years has actually become progressively more risk-averse, which has profoundly affected corporate strategies for drug discovery and development, the rate at which new drugs appear in the marketplace and patients' access to them (see REFS 7,8 for further discussion of this topic). Indeed,

recent criticism from Congress, the media and others regarding drug safety has caused an already risk-averse agency to become even more conservative and defensive in its decision-making. In September 2006, Genentech announced that approval of its colon cancer drug bevacizumab (Avastin) for breast cancer would be delayed by at least a year because of requests from the FDA for additional data. The company said that regulators appeared to be increasing the stringency of requirements for certain types of clinical trials and had arbitrarily demanded that its trials be "audited and summarized" in a way that was different from an earlier agreement with regulators[9].

Regulators moving the goalposts in the middle of the game is particularly vexing for drug developers, and the example with bevacizumab is not an isolated case. Another recent and particularly problematic example involves Somaxon Pharmaceuticals testing an already approved drug, doxepin, for a new indication. The drug, approved for the treatment of depression since 1969, is being tested in very low doses for use as a sleeping pill. The FDA initially assured the company that it could begin human clinical trials without first doing animal tests because of doxepin's long history of use in people and because Somaxon was using only about 1–8% of the dose used to treat depression[10]. However, in May 2006, after having completed several clinical trials, representatives from Somaxon met with the FDA to discuss the submission of a new drug application, and regulators unexpectedly asked for a full battery of testing in animals, which will delay the company's application by at least 6 months[10]. Animal testing is usually considered to be 'preclinical', so it is difficult to understand the logic of animal testing for an almost 40-year-old drug that is undergoing trials for a new indication, and at a far lower dose than it is normally used.

In addition, a number of drugs previously granted marketing approval in Europe have received 'approvable', instead of approval, letters from the FDA, meaning that additional data are required before the drug can be marketed. These include Sanofi-Aventis's rimonabant (Acomplia) for weight loss and cessation of smoking, NPS Pharmaceuticals' recombinant parathyroid hormone (Preos) for osteoporosis, and Encysive Pharmaceuticals' sitaxsentan (Thelin) for pulmonary hypertension.

A further sign of greater risk aversion is the increasingly aggressive use by regulators of post-marketing 'risk minimization action plans' (RiskMAPs). These RiskMAPs can include the submission of additional safety information, including larger safety studies to screen earlier for relatively rare potential adverse reactions, greater restrictions on distribution and advertising, and so on. In March 2005, for example, the RiskMAP that accompanied the FDA's approval of the diabetes drug pramlintide (Symlin; Amylin) prohibited the company from conducting any direct-to-consumer advertising or journal advertising for 1 year following approval, and also restricted promotion primarily to physicians who specialize in diabetes management and who are supported by certified diabetes educators. Brown and Johnson argued persuasively in a 2006 Washington Legal Foundation 'Legal Backgrounder' that this kind of regulatory expansionism is unwise, outside FDA's statutory authority and unconstitutional. They characterized the FDA's ban on advertising as "nothing more than an effort that seeks to keep people in the dark for what the government perceives to be their own good — a concept the Supreme Court has warned courts to view with skepticism."[11] Moreover, they point out that the FDA's ban on advertising Symlin conflicts with the FDA's own guidance to industry, in which the FDA cited "promotional techniques such as direct-to-consumer advertising highlighting appropriate patient use or product risks" as an example of how to use a RiskMAP[12].

This sort of inconsistency from the FDA, which is particularly problematic for companies that have invested substantial sums in R&D, is not uncommon. Regulators' recent actions on the post-approval risk management of two drugs, natalizumab and rituximab (Rituxan; Genentech/Biogen Idec), are illustrative.

In late 2004, natalizumab was approved for multiple sclerosis, a common and debilitating autoimmune disease that affects the central nervous system. The testing of the drug in clinical trials yielded impressive results — the frequency of clinical relapses was reduced by more than half — and led the FDA to grant accelerated approval. In early 2005, however, with several thousand patients already being treated with natalizumab, it was discovered that three had contracted progressive multifocal leukoencephalopathy (PML), a rare and often fatal neurological disorder caused by a virus. (Because the drug suppresses certain components of the immune response, regulators, clinicians and the product's developers were sensitive from the beginning to the possibility of infections as a side effect.) Immediately, the manufacturers voluntarily halted production and distribution and withdrew natalizumab from the market. After the analysis of new safety data, an FDA advisory committee recommended natalizumab's return to the market with revised labelling, but the FDA went far beyond adding more prominent warnings about the drug's side effects to the labelling (which would arguably have been sufficient) and insisted instead on a complex RiskMAP that imposes onerous restrictions on the use of natalizumab. They include limited distribution and additional education and monitoring requirements for patients, prescribers, pharmacies and infusion centres.

Like natalizumab, rituximab, a treatment for rheumatoid arthritis and certain kinds of lymphomas, acts by suppressing elements of the immune system and has also been linked to PML; there have been 23 confirmed cases of PML in patients receiving rituximab for the approved indication of non-Hodgkin's lymphoma and, most recently, 2 cases in patients being treated experimentally for systemic lupus erythematosus. But, in contrast to natalizumab, rituximab has never been subject to a RiskMAP. And in spite of the new cases of PML in patients with systemic lupus erythematosus — and the fact that rituximab also is under consideration for treatment of multiple sclerosis — the FDA was content merely to update the package insert for rituximab. Leaving aside the question of whether rituximab should be subject to a more restrictive RiskMAP or whether natalizumab deserves a less restrictive one, the point is that the FDA's inconsistency sends mixed signals and creates uncertainty — the bane of patients, physicians and drug companies alike.

The Institute of Medicine and the FDA

A report focused on drug safety that was released in September 2006 by the US Institute of Medicine represents the culmination of perceptions that approaches to drug safety need to be fundamentally reconsidered[13]. The report makes sweeping, radical recommendations for change, which in our opinion are not only unlikely to remedy the FDA's current shortcomings, but will make the FDA even more risk-averse, further inflate the costs of drug development, discourage innovation, reduce the number of drugs emerging from the R&D pipeline, and have the net effect of compromising public health.

The proposed recommendations include what would amount to the introduction of only limited approvals for new drugs

during a lengthy period after approval (with special warning labels and restricted direct-to-consumer advertising), greater use of advisory committees, a new registry of clinical trials, and additional resources for the FDA.

Furthermore, under proposals for the disclosure of information about clinical trials that have come from both the Institute of Medicine's report and Congress, the FDA would force drug developers to include details such as timelines, milestones and end points, which drug companies (and current federal law) consider to be sensitive, proprietary information. Such mandatory disclosure would give competitors an early look at sensitive data, thus expropriating from drug developers some of their proprietary information. The prospect of 'competition via forced disclosure' would further reduce the incentive to develop new drugs.

The FDA had anticipated the calls for reform with initiatives of its own to increase the surveillance and reporting on the safety of drugs. These include the creation of a Drug Safety Board, whose objectives are "to provide oversight and advice to [Center for Drug Evaluation and Research] leadership on the management of important drug safety issues and to manage the flow of emerging safety information to healthcare professionals and patients"[14], and a number of projects under the remit of the Critical Path Initiative. These projects include much needed improvements in the FDA's Adverse Event Reporting System and research on animal models for human disease, cardiovascular biomarkers and the genetic basis of adverse events.

Other initiatives, such as the FDA's Drug Watch Program, appear to have more to do with public relations than public health. In May 2005, the FDA published draft guidance on the Drug Watch Program, which will make 'emerging safety information' publicly available. According to the FDA[15], the Drug Watch Program:

> *…is intended to identify drugs for which FDA is actively evaluating early safety signals. The Drug Watch is not intended to be a list of drugs that are particularly risky or dangerous for use; listing of a drug on Drug Watch should not be construed as a statement by FDA that the drug is dangerous or that it is inappropriate for use. Rather, inclusion on the Drug Watch signifies that FDA is attempting to assess the meaning and potential consequences of emerging safety information.*

The FDA further notes in the same document that the Drug Watch Program is intended:

> *…to share emerging safety information before we have fully determined its significance or taken final regulatory action so that patients and healthcare professionals will have the most current information concerning the potential risks and benefits of a marketed drug product upon which to make individual treatment choices.*

It is difficult to predict what physicians and other health-care providers — let alone members of the public — will do with such preliminary data, which are available on the FDA's web site. There is a difference between indiscriminate data and useful information, and the Drug Watch Program seems destined to provide far more of the former than the latter. Then-FDA Deputy Commissioner Scott Gottlieb addressed that point: "Information that could influence clinical medical practice needs to be made available more quickly, and more widely, after it has gone through a deliberative scientific process that firms up its meaning and the magnitude and the veracity of its conclusions."[16] But Gottlieb himself characterized the information that would appear on Drug Watch as data that are "still un-scrubbed by scientific rigor."

Moreover, given the current desire at the FDA for ways to demonstrate a commitment to drug safety, and the difficulty of proving a negative, how will a 'suspect' drug ever be able to clear its name and get off the Drug Watch list? Surely, it would be far more constructive to update product labelling continuously and rapidly — which can now be accomplished using the FDA's web site and e-mails to health-care providers and consumers — once regulators are past the stage of merely "attempting to assess the meaning and potential consequences of emerging safety information," and have actually "determined the significance" of the information.

In January 2007, the FDA announced a plan to carry out a comprehensive assessment of the safety of some new drugs within 18 months of their introduction, and to issue a 'report card' on their performance. Although this may sound plausible, it appears to be inconsistent with the data cited above which show that in fact newer drugs confer an advantage over older ones in reducing mortality. And in February 2007, in reaction — many observers would say overreaction — to proposed legislation, the FDA introduced new restrictions on members of advisory committees, which are composed of outside experts. Committee members who receive money from a drug or device maker would be barred for the first time from voting on whether to approve that company's products; and if they receive more than $50,000 from a company or a competitor whose product is being discussed, they would no longer be allowed to serve on the committees. This eliminates precisely those experts who are likely to possess the greatest expertise about the subjects under discussion; disclosure of potential conflicts of interests and recusal when appropriate would have been far better than the new, rigid, one-size-fits-all automatic exclusions and disqualifications.

Congressional confusion

Over the past few years, Congress has weighed in with a variety of proposals that were supposedly intended to enhance drug safety, including the creation of an independent agency concerned specifically with drug safety. Most of these proposals were ill-conceived.

An agency concerned only with drug safety would place us in the realm of regulating according to the bogus 'precautionary principle', which erects high barriers to new products, processes and technologies, whatever their potential benefits. Were this new agency to be created, it would effectively create within the FDA an anti-drug entity with strong incentives to argue for the non-approval or withdrawal from the market of drugs that have significant side effects even if they offer huge net benefits. (We have seen this already from certain factions within the FDA.) At the least, the net effect would be to make the FDA's drug evaluators even more defensive and risk-averse. Fewer drugs would be approved and more would be subject to dubious withdrawals from the market; and with these increases in development 'failures', the average cost to bring a new drug to market would rise even further, diminishing the robustness of the drug development pipeline.

Congressional meddling in the conduct of clinical trials has been particularly ill-advised. For example, in response to a long history of less representation of women and minorities in clinical trials (often for good reason, such as a reluctance to expose women of childbearing age to experimental drugs), Congress passed a law in 1993 requiring their inclusion in federally funded clinical trials in numbers that are

"sufficient to provide for a valid analysis of any differences … in response to drugs, therapies and treatments."[17] If this were enforced strictly, it could raise the numbers of subjects in clinical trials — and the attendant costs — substantially. Moreover, although one-size-fits-all requirements of that kind might seem to offer clarity, they are fraught with all sorts of challenges, such as whether every minority group must be represented. Although regulators have not enforced such quotas, their enshrinement in law remains a concern. The strict interpretation of legislation does not always permit the interposition of common sense, and the requirements could easily be enforced in the future as the result of litigation or congressional oversight hearings.

What is the price of safety?

Defenders of the present, risk-averse system argue that lower efficiency is the price of safety. But this is a false trade-off. High standards of safety and greater efficiency could be achieved if we were to reform fundamentally the way drugs are regulated. If we could end regulatory excesses (especially those that are politically driven) and introduce competition into regulatory oversight, more patients would benefit from the greater number of drugs made available to them in a timelier way (for further discussion of this proposal, see REFS 7,8).

Indeed, in contrast to the perception that speedy reviews compromise drug safety, a recent study of the effects of the Prescription Drug User Free Act (PDUFA) — which requires drug sponsors to pay fees to the FDA for the timely review of new drug applications (NDAs) — not only indicates that is this not the case, but provides evidence of the benefits of rapid reviews to public health. The study assessed the trade-off between the benefits of getting 'good' drugs on the market more quickly versus the advantages of preventing 'bad' drugs from getting on the market[18]. The researchers estimate that by shortening the time the FDA took to approve drugs (by providing more reviewers and committing the FDA to certain statistical milestones), the PDUFA significantly improved the situation both for patients and for drug producers. According to their calculations, this benefit, or 'social surplus,' was in the range of $18–31 billion. Converting these economic gains into equivalent health benefits, they found that the faster access of drugs to the market made possible by PDUFA's additional resources and reforms saved the equivalent of 180,000–310,000 life-years[18].

The researchers also took into account the possibility that the faster approval times mean more unsafe drugs on the market. However, they found no statistically significant difference in the proportion (2–3%) and timing of withdrawal of drugs that were approved before and after the PDUFA. To investigate further the relationship between faster approval times and drug safety, they assumed that without the PDUFA, none of the drugs actually withdrawn for safety reasons would ever have been allowed in the first place — a 100% ability of regulators to detect what will turn out to be hazardous products. In other words, they used the upper bound on the negative impacts of the PDUFA caused by drugs ultimately withdrawn for safety reasons. Even with this extreme assumption, they found that 55,600 life-years were lost owing to speedier approval, only 18–31% of the benefits[18].

> "The FDA could contract out product reviews — which has been highly successful in pilot programmes."

We would offer several caveats about the presumptive benefits of the PDUFA, which is still in effect and is widely expected to be reauthorized, with higher user fees, in 2007. First and foremost, the speed of approval measures only the relatively brief time span between the submission of an NDA or a biologics license application (BLA) for review and the FDA's approval. However, most of the pre-approval time that a drug is under the FDA's jurisdiction is the investigational new drug phase: the much longer interval between the initiation of clinical testing and the submission of the NDA or BLA, which can last for a decade or more. Second, given that the benefits of speed in the above study were measured relatively accurately but the costs of speed (that is, the benefits of slowing down) were explicitly overstated, a reasonable conclusion is that even with the PDUFA, the time between the submission of the application and its approval is still too long. Finally, presumably the same benefits of more rapid approvals could have been obtained if the additional resources had been provided to the FDA by congressionally appropriated funds instead of by PDUFA user fees, which are nothing more than a discriminatory tax on a single industrial sector.

Potential for reform

Although any system of drug oversight should preserve a reasonable degree of confidence in product safety and efficacy for the indications listed on the label, such assurance can be obtained not only through federal regulation but also from the evolving interplay among industry, government, academia, medical practice, insurers and the courts. Since the current framework for the regulation of new drug development was put in place more than four decades ago, basic and clinical research techniques have advanced, the public's sophistication and awareness about drugs have grown, and the media have become both more aggressive and more attuned to health issues. In addition, pharmaceutical marketing, tort case law and the system for cost-reimbursement for medical treatments have all evolved. These factors have altered the nature of manufacturer–physician–insurer–patient relationships profoundly and have superimposed new layers of scrutiny and control upon the FDA's evaluation, approval and monitoring activities.

There are many more professional, full-time, career clinical researchers now than in the 1960s, and also more proficient, for-profit clinical research organizations that design and perform clinical studies for drug sponsors. In addition, there are additional institutional safeguards to patients, such as corporate procedures for carrying out and overseeing clinical trials and conducting post-marketing drug surveillance, and the government-mandated institutional review boards in clinical research institutions. The reporting of adverse events has been vastly improved, and the science of pharmacoepidemiology systematically examines adverse events in exposed populations.

But the most profound changes have resulted from the evolution of various non-governmental entities into *de facto* drug-vetting, standard-setting organizations. The newest and most potent of these are managed-care organizations, which exercise their influence through large-scale purchasing, construction of formularies, monitoring and drug use review. The ability of physicians who practise within organizations such as health-maintenance organizations to prescribe is increasingly affected and constrained by computerized systems that perform overall integration of the medical record for case management. A physician can be prevented from prescribing medication if, for example, according to computerized monitoring of their decisions, the drug is inconsistent with a patient's

listed diagnosis; excessive in dose, frequency or length of administration; likely to interact dangerously with another medication the patient is taking; or even judged not to be cost-effective compared with alternative drugs. Drugs can be omitted or removed from formularies if cheaper alternatives are available or if they are deemed to be non-essential because they treat 'non-disease' conditions such as baldness or skin wrinkles. In short, the health-maintenance organization or insurer has become a third gatekeeper — along with the FDA and the prescribing physician — between the manufacturer and the patient.

These various influences work together to protect the integrity of the clinical trials and, after approval, to assure product safety, efficacy and effective post-marketing surveillance. The operation of these factors diminishes the relative importance of the FDA as the protector of the patient. But instead of a diminution of the FDA's power, responsibilities and requirements, we have seen the opposite; and, as discussed in the previous section, the pendulum seems to be currently swinging even further in that direction. Regulators now make decisions defensively — in other words, to avoid approvals of harmful products at any cost, they tend to delay or reject new products. That's bad for public health, for drug developers, for consumers' freedom to choose and for patients' well-being. The FDA is not unique in this regard. All regulatory agencies that perform pre-market evaluations are subject to criticism if dangerous or questionable products make it to market (often even for products that offer net benefits), but actions that keep beneficial products from reaching consumers seldom receive attention, let alone condemnation.

Routes to reform

Meaningful change in the United States will require legislative action, but recent congressional interest in drug regulation has taken the form of politically motivated investigations of supposed under-regulation or insufficient attention to product safety. Ironically, it is Congress's failure to carry out its oversight and legislative role responsibly that has permitted the risk-averse culture at the FDA to become progressively worse and more entrenched. So, what could be done to address this situation?

As discussed above, the FDA has already begun to improve the post-marketing surveillance of adverse reactions to drugs but has yet to address the culture of risk aversion that unnecessarily delays product approvals. The FDA could contract out product reviews — which has been highly successful in pilot programmes[19] — and the accumulation and analysis of safety data, and Congress could create extra-governmental mechanisms for product oversight. For example, the regulation of medical devices (and many other consumer products) in the European Union relies heavily on product standards but normally does not directly involve government regulators in product review. For low-risk devices, manufacturers themselves are allowed to certify that their products meet the necessary standards. For higher-risk products, manufacturers must obtain third-party review from private-sector, profit-making entities (notified bodies) that test products, inspect manufacturing systems and ultimately verify that EU standards have been met[20]. Another apposite model is the Nationally Recognized Testing Laboratories in the United States, the prototype of which is Underwriters Laboratories, a private, non-profit entity that crafts standards and certifies compliance with them for tens of thousands of categories of consumer products ranging from lighting fixtures and flame-retardant chemicals to bulletproof glass.

> "Reformers often are accused of being beholden to drug manufacturers, and of plotting to deregulate, which is seen as a conspiracy among political reactionaries and free-market fanatics."

In addition, the FDA's senior and mid-level managers should be made more accountable — especially for scientifically dubious policies and needless delays in getting new drugs, vaccines and medical devices to patients who need them. One way to achieve that would be to create an independent, strong ombudsman mechanism that could impose negative sanctions on civil servants who are incompetent, indolent or insubordinate. By contrast, all of the newly introduced checks on the FDA's drug approvals — such as the Drug Safety Board and the Drug Watch Program — and more recent proposals along these lines are asymmetrical, in the sense that they primarily address narrowly defined concerns about safety, but do not address the lost benefits of drugs that are needlessly delayed or abandoned.

Conclusions

By means of policies that include the funding of research, protection of intellectual property, establishment of price controls, and pre-market and post-approval regulation, governmental influences on the discovery, development and marketing of new medical devices and drugs are profound. Regulatory policies and decisions are especially potent, spelling life and death for patients and companies alike. Those who disagree with regulators' actions are largely without recourse; the courts consistently defer to the presumed disinterested expertise of the regulatory agencies.

Many lives would be improved and saved by a more efficient system of oversight. Why, then, is there no sense of urgency, no lobbying for regulatory reform from any prominent quarter or interest group? The reasons are complex. Would-be reformers often are accused of being beholden to drug manufacturers, and of plotting to deregulate, which is seen as a conspiracy among political reactionaries and free-market fanatics who favour commerce over the protection of public health. Paradoxically, even the largest pharmaceutical companies fail to lobby for reform, either individually or through their trade associations. How can that be?

First, drug companies continue to be profitable. For them, the vast expense of regulation is simply part of the cost of doing business. Their own massive regulatory-affairs bureaucracies are, to some extent, special interests convinced that they would not be well served by less regulation. Moreover, up to a certain point, excessive, expensive, inflexible regulation is advantageous to larger companies because, owing to 'economies of scale' and greater experience with compliance, it discriminates against smaller companies, which increasingly are the principal innovators in drug development. Smaller companies feel the burden of excessive regulation (including user fees) and shifting goalposts more acutely and are more eager for regulatory change. But even for them regulatory reform is, at most, a long-term strategic goal, and they tend to be more concerned with day-to-day technical and financial crises. Individually they are ill-equipped — and probably ill-advised — to criticize and antagonize the regulators who have so much discretion over the testing and marketing of their products. Trade associations are in a better position to be aggressive, to pressure regulators for reforms or other concessions (as, unlike individual companies, they are largely immune from retribution), but the two main US-based

trade associations that represent pharmaceutical companies — the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Industry Organization (BIO) — are dominated by large companies that are relatively content with the status quo.

Second, in spite of all the obstacles, entrepreneurial ingenuity combined with technological innovation continues to spawn new companies. Even as the industry has carried out a series of mergers to create mega-companies during the past decade, a wave of new start-ups has launched with each new technology or scientific breakthrough. Entrepreneurs created new companies to exploit recombinant DNA technology and hybridoma technology in the 1970s. More recently, they created new companies to take advantage of genomic, proteomic and metabolomic data, antisense technology, human gene therapy and RNA interference (RNAi), and to develop 'individualized therapies'. Because the ultimate rewards are potentially great, even imposing regulatory obstacles cannot extinguish the drive to create, compete and succeed in this field. However, there would be more, and greater, successes if the regulatory barriers were less imposing and more creatively constructed.

For reasons that are equally complex and multi-factorial, the public are as passive as the drug companies about regulatory reform in the United States. Although they are literally dying for it, the ageing American population are not clamouring for a more streamlined, responsive system that will offer them more new drugs sooner and at lower cost. For one thing, few Americans now pay the full costs of pharmaceuticals out of pocket. A significant proportion of prescription drug costs is defrayed by some kind of third-party payer, usually a managed-care organization, insurance company or the government. Therefore, individuals who need expensive new drugs seldom experience the full impact of inflated prices at the pharmacy.

A third factor, which affects the public's view of regulation and regulatory reform, harkens back to the asymmetry described above. The public is made aware of approved drugs that manifest problems (or alleged problems) but does not know about — and therefore is not concerned about — drugs that have never been developed at all because of regulatory barriers to innovation.

Fourth, as far as most of the public is concerned, the nuances of drug development and its regulation are arcane and obscure. For example, many people assume that the FDA actually carries out the testing of pharmaceuticals, but it does not: regulators only evaluate data generated and submitted by industry. And the media have done little to educate them, too often evoking interest in regulatory affairs only during a crisis — or what it can portray as one.

Most importantly, at any given time, most Americans are healthy. They tend not, therefore, to pay attention to the fact that the quest for zero risk systematically prevents them from getting drugs that they might need in the event of injury or illness. And even if they were aware of this regulatory bottleneck, the lack of FDA and congressional accountability means that they can do little about it. Such impotence, in turn, offers them little incentive to become informed and involved. Even the few consumers who have a rudimentary understanding of who does what, when and to whom during drug development tend to be fearful about new products. Many Americans have become conditioned to seek technological innovation that is completely risk-free, and they seek someone to blame when it is not. Their innumeracy and lack of understanding about trade-offs among different sources of risk makes them highly susceptible to misleading information from those who regularly raise false alarms and demand that regulators ban, withdraw, limit and restrict many useful products.

These factors combine to confuse consumers and make them hesitant even to endorse, let alone demand, significant regulatory reform. Not realizing that there is a point of vanishing returns that we have passed, they believe that more regulation must be synonymous with more protection, and that more governmental scrutiny will make us safer and move us ever closer to the Holy Grail of zero risk. In addition, because of the lack of sound, objective, easily accessible information about the potential harmfulness of the regulatory status quo, they exhibit a kind of 'rational apathy', which simply means that in the absence of any obvious and proximate threat to their well-being — and of any likelihood that their actions will change the course of events — it is reasonable for them to remain unconcerned.

Another related phenomenon is that significant societal change seldom occurs except at times of crisis, when ideas have a greater likelihood of consequences. As Nobel Prize winner Milton Friedman and co-author Rose Friedman observe, in a kind of economist's equivalent of the physical property of inertia, "once a tide in opinion or in affairs is strongly set, it tends to overwhelm counter-currents and to keep going for a long time in the same direction. The tides are capable of ignoring geography, political labels, and other hindrances to their continuance."[21] But, the Friedmans continue, the very success of these tides "tends to create conditions that may ultimately reverse them."

No matter how profound the economic and public health costs of over-regulation, and no matter how obvious and persuasive the arguments for regulatory reform, the fundamental changes needed to turn the tide will occur only if the public demands them.

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Competing interests statement
The authors declare no competing financial interests.

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