Virtually all developed countries require drugmakers to demonstrate both the safety and efficacy of their products before approving them for sale. In the United States, this oversight is, of course, conducted by the Food and Drug Administration. And one key decision the FDA faces – arguably, the most central one – requires it to balance conflicting objectives. On the one hand, it is charged with protecting the public from drugs that don’t work as promised or have dangerous side effects. On the other, it is (rightfully) under pressure to speed delivery of lifesaving drugs and, more broadly, to encourage medical innovation.

Critics of the FDA find fault with it from both these polar perspectives. Some have argued that the FDA is taking insufficient time to evaluate new drugs, thereby allowing unsafe drugs to enter the market. One critic, Dr. Sidney Wolfe, the director of the health research group at Public Citizen, the consumer advocacy group, concludes that the
agency’s determination to rush through questionable drugs “makes it look like the FDA is part of the drug industry protection service.”

Others assert that the FDA takes far too long to approve new drugs, undermining technological progress – and, ultimately, the welfare of patients. Robert Higgs, an economist at the libertarian Independent Institute, argues that “Americans would be better off with drastic curtailment – ideally the complete abolition – of the current regulatory regime, which imposes major costs while providing little if any genuine protection of the public health.”

But given the heat of this debate, surprisingly little light has been directed at the realities. Indeed, researchers have not even outlined the ways they would assess whether the FDA has chosen the right balance between caution and innovation. And the cost of our ignorance may be
quite substantial, since the FDA regulates markets that account for about one-fifth of total consumer spending in the United States. Here, we try to fill in the gap – to test the optimality of the speed-safety tradeoff. Our test compares outcomes before and after Washington adopted a new system under the Prescription Drug User Fee Act of 1992, which was in large part intended to reduce evaluation time.

The value of a drug to society consists of the benefits (in terms of extending life and reducing morbidity) that it generates from the time of review and approval to the time of withdrawal – if the drug is, in fact, withdrawn. To estimate the social “surplus” generated by the use of a drug one must go a step further, subtracting the cost of discovering and manufacturing the drug from its gross value to society. As shown in the figure on the next page, this social surplus can be divided between the portion that goes to consumers (the difference between the value of the drug and the price consumers pay) and the portion that goes to producers (their revenue, less their costs). If the drug is beneficial – as it is in the figure – its overall social value falls with the length of the FDA review and rises with the time on the market until withdrawal. Note, however, that if the drug does more harm than good – if the social surplus is negative – delay is a good thing. Hence, in such cases, overall social value rises with FDA review time and falls with the time until withdrawal.

**THE PRESCRIPTION DRUG USER FEE ACT**

First, some background. The idea of charging user fees for services provided by government regulators has ample precedent – think, for example, of the fees long charged to applicants by the Patent and Trademark Office. The Prescription Drug User Fee Act of 1992 authorized the FDA to collect fees from those submitting an application for review of a new drug. The act was controversial, however, in that the amount collected for each application was very substantial. Applications with clinical data were assessed a one-time fee of $100,000, while each supplemental applica-
tion with clinical data, and new applications with no clinical data, cost $50,000. Annual manufacturing establishment fees were set at $36,080, while annual product fees were $6,000. And when the act was amended in 1997, fees escalated sharply. In 2004, for example, applications with clinical data were assessed a one-time fee of $573,500. Waivers and exemptions were granted to small firms, and to sponsors submitting an application under the Orphan Drug Act of 1983, which offers financial incentives to produce drugs with very limited markets.

In exchange for payment of these hefty fees, the FDA is legally obliged to “review and act on” submissions, which are assigned either a standard or priority status, depending in part on the novelty of the therapeutic agent and the existence of unmet medical needs. The FDA is required to deliver a complete review on 90 percent of priority applications within six months. And it is obliged to review 90 percent of standard applications within 10 months.

Note, however, that the law stops short of requiring approvals or final denials in a fixed period. The FDA can issue one of three possible actions by the relevant date. The first is a “non-approvable” letter indicating that the drug has not satisfied the FDA’s standards for safety and/or efficacy. The second is an approvable letter indicating that a drug can be approved if specific deficiencies are remedied. The third is an approval letter that gives the sponsor the right to market the drug.

To assess the act’s impact on actual approval times, we used data provided by the FDA, which indicated that approval times have been falling for quite some time – at least since 1979 – and appears to suggest that approval-time declines have accelerated, particularly before the 1997 amendment. For example, mean approval time from 1979 to 1986 was 33.6 months, 28.2 months from 1987 to 1992, 18.6 months after the law was
passed, and 16.1 months after the law was amended in 1997.

One way of depicting drug-approval time trends is to construct “survival” curves that plot the proportion of approvals not yet completed within a fixed time period. The survival curve shown in the figure plots the percentage of approvals remaining over time with one curve for each of the periods 1979 to 1986, 1987 to 1992, 1993 to 1997 and 1998 to 2002.

The more-rapid decline in survival curves during the act’s first decade, compared to pre-act curves, indicates faster approvals. Note that the horizontal line designated with a 90
percent rate in the graph intersects the various survival curves at far longer time periods than those stated by the act’s goals, since it mandates involved review times rather than actual approval times.

To estimate the law’s quantitative impact, we compare review times before and after its passage using 662 New Molecular Entity (NME) drug approvals by the FDA from 1979 to 2002. Before the act, review times were declining at about 2 percent a year. Passage and implementation of the act and the 1997 changes accelerated the decline by 6 to 7 percentage points and 3 to 4 percentage points a year, respectively. We are then able to estimate how much longer approvals would have taken in its absence.

The estimated impact on review times induced by the act are first used to assess the impact on producer surplus. The revenues from a drug under the act are derived from actual sales data, while the hypothetical revenues if it had not been in force are estimated from the extra time we infer that it would have taken to review the drug. To estimate the act’s effect on the private innovative return of the drug, we must also net out the extra user fees charged for accelerated reviews, as well as the cost of manufacturing the added volume of product. Our main finding is that the act increased producer surplus by about $11 billion. For the sample of 284 drugs for which we had sales information during the act’s first decade, this represents a gain of about $39 million per drug launched.

To estimate the total change in social surplus linked to the act, we need to add an estimate of the change in consumer surplus to the change in surplus going to producers. This cannot be derived solely from sales figures, however, since the price paid for a product reflects only a portion of its actual value to the individual.

Thus, an affluent patient with a bacterial infection might pay just $100 for a lifesaving round of antibiotics, but would, if necessary, have paid $100,000 to get the job done. As a practical matter, consumer surplus is determined by the shape of the demand curve for the product, the degree of market power the seller can exercise and the degree to which the seller is able to price-discriminate – that is, to charge different prices to customers who value the product differently.

Even in an extreme case in which the seller could extract every bit of surplus from consumers by charging a different price to each one, the expiration of the patent on the drug
would mark the beginning of competition among generic versions – which, in turn, would inevitably lead to the generation of consumer surplus.

Our major finding here is that the added social surplus created by the greater speed is between $18 billion and $31 billion, where the difference represents extreme assumptions about market conditions. For the 284 drugs introduced since the act’s inception, these upper and lower bounds on the social surplus amount to a gain of between $62 million and $109 million per drug.

That’s the gross benefit from accelerated drug review. To calculate the net benefit, we need to subtract the social costs of increasing the risk that a dangerous drug slips through the review process. To assess the impact on consumer safety, we consider the effect the act had on the fraction of drugs eventually withdrawn from the market for safety concerns, along with how rapidly they were withdrawn. By the most plausible measure, the act did not, in fact, have any effect on drug safety: neither the proportion of drugs eventually withdrawn (2 to 3 percent), nor the speed with which they were withdrawn, changed in any statistically significant way since the law’s passage.

It’s still possible, though, that, other things being equal, the review process was becoming better at weeding out dangerous drugs before approval. Thus, no change in safety from before the act was passed to afterward might imply some cost to the limitations on safety imposed by accelerated review. Hence, for the sake of argument, we compute an extreme upper bound on the adverse safety effects the act induced by assuming that all drug withdrawals after 1992 were due to errors induced by the review speedup, and that there were no benefits associated with these drugs before they were withdrawn. Using this extreme as-

<table>
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<tr>
<th>DRUG NAME</th>
<th>NUMBER OF DEATHS</th>
<th>LIFE YEARS LOST</th>
<th>COST AT $100K PER LIFE YEAR ($M)</th>
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<tr>
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ESTIMATED COST OF DRUGS WITHDRAWN FROM MARKET THAT WERE SUBMITTED FOR ACCELERATED REVIEW
sumption, we find that the drugs approved and withdrawn since the law was enacted cost, at most, about 56,000 life-years in avoidable deaths.

To generate a comparable figure for the gains in health implicit in the greater speed the law generated, we divide estimates of the social surplus linked to it ($18 billion to $31 billion) by the lowest estimate of the value of a life-year ($100,000).

This latter figure was derived from studies in which value of life is inferred from how much income workers are willing to forego in order to reduce the risk of fatal accidents, or how much consumers are willing to pay for marginal improvements in the safety of homes, cars and the like. The calculation implies that the act added 180,000-310,000 life-years – far more than the 56,000 life-years lost if, in fact, it was responsible for all the mistakes of the drug review process.

**SOME PERSPECTIVE**

By one interpretation, the analysis suggests there was no trade-off between safety and speed: the increased speed in reviewing applications had no measurable impact on the quality of the review process. But even if there was a price – that is, if hanging on to review procedures before 1992 would have reduced errors that led to deaths – there are very good reasons to believe that the price was worth paying. Faster access to new drugs saved more lives than the release of dangerous drugs could possibly have claimed.

More to the point, in a world of finite resources, people are effectively forced to place a finite value on their own lives. And the value they placed on accelerated access to new lifesaving and life-enhancing drugs far exceeded the highest estimate of the cost in terms of greater risk of premature death and morbidity. Indeed, the value of accelerated review was so great that one must ask whether additional measures – measures that actually did allow more bad drugs to make the cut – would be justified.

The catch, of course, is that neither the public nor the politicians who represent them have openly acknowledged the relevance of cost-benefit analysis in the context of life-and-death medical-policy decisions. Are Americans willing to sacrifice statistical lives in order to maximize an abstraction like social welfare? Perhaps not. But until the debate over prescription drug regulation is put in cost-benefit terms, drug policy is bound to fail society’s most basic needs.