COST OF CAUTION:
The Impact on Patients of Delayed Drug Approvals

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The Food and Drug Administration (FDA) has long been judged by how well it balances the goal of safer and more effective prescription drugs with the higher costs that extended reviews impose on products coming to market. Public discussion of regulatory delays has focused mainly on the costs to companies, and the extent to which these costs might reduce the stream of potentially important new drugs.

But what about the cost of protracted regulatory drug review to patients who stand to benefit? This study attempts, for the first time, to assign a price to those unrealized benefits—specifically, the value of longer lives. It argues that the cost to patients is not only considerable, in terms of the monetary value to patients of earlier treatment, but exceeds the costs to prescription-drug developers, which typically spend $1 billion on researching, developing, testing, and marketing every approved drug. In other words, a regulatory review process that was, first of all, efficient and second, as cognizant of benefits denied as it was of risks posed, should not be one that was unreasonably cautious or slow.

This study examines three classes of approved and marketed drugs that have proved to possess significant medical value: highly active antiretroviral treatment (HAART), for the treatment of HIV/AIDS; trastuzumab (Herceptin), for the treatment of breast cancer; and rituximab (Rituxan), for the treatment of non-Hodgkin’s lymphoma. It found:

- To an HIV/AIDS patient being treated with HAART, a year’s earlier access would be worth $16,000, and $46,000 for three years’ earlier access. To the entire cohort of such patients, the value of one year’s earlier access would be $19 billion. The value of three years’ earlier access would be $53 billion.

- To the entire cohort of breast cancer patients being treated with trastuzumab, the value of one year’s earlier access would be $8 billion. Three years’ earlier access would be worth $22 billion.

- To the entire cohort of patients being treated with rituximab for non-Hodgkin’s lymphoma, a year’s earlier access would be worth $310 million. Three years’ earlier access would be worth $850 million.

By contrast, shortening Phase III clinical trials by one year would save the typical drug company only about $40 million. The release of HAART one year earlier would have increased the profits of the firm marketing it by $4 billion, or 14 percent, about a fifth of its value to AIDS patients. Had the impact of the three drugs on patients’ quality of life been measured, the figures would be even more impressive.

All three of the drug classes studied are particular success stories, and were chosen to demonstrate the cost that delay can exact from patients with life-threatening diseases. The large discrepancy between the value of HAART and that of the other two drugs reflects both the lower incidence of the diseases they treat and their smaller impact on longevity.

In addition to changes in the FDA’s own deliberations, certain practical steps can be taken to expedite the regulatory process. As the result of adding reviewers to the staff of the Food and Drug Administration, under authority of the Prescription Drug User Fee Act, for example, the period from synthesis to commercial distribution became shorter. To the extent they can be implemented without unduly sacrificing safety, the authors would like to see these other reforms tried:
• **Allowing the payment of stipends to clinical-trial volunteers.** Doing so, after obtaining informed consent, would address the paralyzing shortage of volunteers.

• **Relying on biomarkers.** Biomarkers are byproducts of disease processes (such as elevated numbers of CD4 cells in AIDS cases) or indicators of disease risk (such as cholesterol levels). Their use would allow researchers to estimate the likelihood of a treatment’s success before completion of full clinical trials.

• **Offering FDA regulators performance incentives.** These could expedite the identification of promising new treatments or the evaluation of new guidelines for clinical trials.

• **Establishing an ombudsman.** Such an official would review the impact of FDA regulations and practices on drug-development times.

The FDA’s pursuit of these and other measures, in addition to its incorporation of this paper’s findings into its assessment of candidate drugs’ potential benefits and risks, should lead to the earlier availability of effective treatments for life-threatening illnesses.
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INTRODUCTION

Health is wealth, or so it would seem on the basis of a research finding that gains in income over the course of the twentieth century were matched by gains in the economic value of improved health over the same period (Nordhaus 2003). Those in the century’s last decades especially were enormous. The dollar value of increases in longevity between 1970 and 2000 was over $3.2 trillion per year, equaling one-half of average annual GDP during that period (Murphy and Topel 2006). Even seemingly modest gains can be meaningful; for example, a 1 percent reduction in Americans’ mortality from cancer may be worth as much as $500 billion.

Much of this gain was arguably the result of medical research and development. For example, Rosen et al. found that new procedures and drug treatments for heart attacks (acute myocardial infarctions) reduced the two-year death rate from the disease by nearly 20 percent (Rosen et al. 2007). Similarly, Sun et al. found that improvements in cancer treatment accounted for the vast majority (79–85 percent) of gains in rates of cancer survival between 1988 and 2000 (Lakdawalla et al., forthcoming).

Pharmaceuticals and biotech medicines, in particular, are playing an increasingly important role in medical innovation and patient care.
One dramatic example is human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). The development of highly active antiretroviral therapy (HAART) in 1996, it was estimated, produced nearly fourteen years of increased life expectancy (Philipson and Jena 2006). Similarly, the introduction of rituximab (Rituxan) dramatically improved the survival rates of patients with non-Hodgkin’s lymphoma (see Molina 2008), while trastuzumab (Herceptin) has produced similar effects for patients with certain forms of breast cancer (Piccart-Gebhart 2005, Romond et al. 2005, Hortobagyi 2005).

New drugs, even ones that do not perform miracles, are generally superior to older ones. Columbia University economist Frank Lichtenberg, for example, has shown that patients living in states offering faster access to these new drugs lived longer and showed slower growth in disability rates than patients in other states, even after accounting for patients’ risky behaviors and other variables. Lichtenberg also found that for every dollar that Medicare spends on newer medicines, it saves six dollars in other healthcare costs, primarily by reducing the need for the services of physicians and the incidence and length of hospitalizations (Lichtenberg 2010).

However, patient access to newer medicines is limited by a complex, expensive, and ever-lengthening drug-development process. Well-known studies from the Tufts Center for the Study of Drug Development have found that the period from the inception of research into the formulation of a molecule until approval by the Food and Drug Administration for marketing is currently about twelve years, two-thirds of which is consumed by clinical trials (whose scope is dictated by the FDA) as well as the FDA’s own approval process (Dimasi et al. 1991, 2003). Observers hold various factors responsible—for example, the pharmaceutical industry’s recent focus on complex chronic diseases such as Alzheimer’s and certain forms of cancer, which may have multiple genetic and environmental causes.

As for the delays caused by the FDA, some may be the result of excessive premarket testing. These tests may be unreasonably time-consuming and redundant. Sometimes, they keep helpful drugs off the market; yet they still may not be comprehensive or sophisticated enough to expose rare side effects produced by drugs that are approved.

The newer these drugs are, the more expensive they are to develop. For instance, studies conducted at Tufts have estimated that the cost of developing a single successful drug increased from $413 million (in 2003 dollars) three decades ago to roughly $939 million today (Dimasi et al.). These studies’ working definition of the cost of drug discovery is limited to actual R&D outlays, taking into account the cost of capital.

The approach used by Tufts to calculate R&D costs implies that delays in drug development and approval reduce their present value, assuming fixed costs before market entry are extended further into the future. (Inflation works similarly, by reducing the value of a debt when the period over which payments are made is extended but the amount of each payment remains the same.) In fact, delays may do the opposite, by pushing profits further into the future as well.

The most exorbitant costs, however, lie elsewhere. The major argument in this report is that the Tufts calculations do not fully capture the costs to patients of potentially avoidable delays in the regulatory process. The cost to patients has both a direct and an indirect aspect: the first, in the form of shortened life spans and lower quality of life resulting from delays in obtaining helpful drugs; and the second, in the form of curtailed R&D, resulting in the loss of industry profits, some portion of which would go toward underwriting the cost of discovering the next generation of helpful drugs. To quantify these “invisible” costs, we, for the first time, measure the losses incurred by patients dying before drugs that could have helped them entered the market.

**THE PERILS OF DELAY**

The FDA’s mission is not only to bring safe and effective drugs to market but, as it notes in its mission statement, to help “speed innovations that make medicines and foods more effective,
safer, and more affordable.” In almost every decision that the FDA makes, it has to confront the trade-off between safety and availability, since no drug or medical device is safe for everyone under all circumstances. Delaying access to new drugs by requiring companies to conduct additional tests or clinical trials may allow the agency time to accumulate more evidence on the drug’s safety, but it also slows access to the drug by patients who might benefit from it. Conversely, expedited access may expose consumers to unknown risks.

But the harm that results from delaying or denying access to a beneficial treatment is less apparent than the harm that occurs when a drug producing serious side effects is mistakenly approved for sale. Accordingly, an excessively cautious FDA is likely to be considered by policymakers and the public no worse than prudent, while regulators will be judged careless (or worse) when rare side effects emerge and harm patients. For these reasons, many economists and policy analysts believe that the FDA usually errs on the side of caution, even though such a policy may result in greater suffering than a more active or lenient one. Copland and Howard (2009) elaborate:

“At Type I” error [involves] approving a drug as reasonably safe that later turns out to be unsafe or ineffective; and “Type II” error [involves] withholding from the public a drug that is reasonably safe and effective.

The Type I error, insofar as it results in widely publicized deaths or serious injuries after a drug is approved for sale, is of greater public concern and consequently has the greater impact on agency oversight by Congress. Exemplifying the Type I error is the history of thalidomide, a sedative that was widely marketed in Europe and Japan (but not the United States) to treat pregnancy-related nausea (“morning sickness”) before it was discovered that it caused severe birth defects. The thalidomide tragedy led in 1962 to passage of the Kefauver Harris Amendment, which created what became the FDA’s current drug-approval regime.

Although no one can deny that the FDA’s caution in evaluating thalidomide prevented the tragedies that occurred overseas from repeating themselves here, it is also the case that since the thalidomide affair, other drugs safely and effectively used by thousands of consumers in other countries for years were kept off the market in this country, forcing prudent but needy Americans to obtain these drugs abroad or illegally import them.

Growing awareness of Type II errors throughout the 1970s and 1980s, particularly in the case of drugs treating life-threatening illnesses such as AIDS and cancer, eventually led to congressional and FDA reforms designed to accelerate agency review of certain types of treatments. These reforms recognized that the good that such drugs could do for particularly distressed patients lacking effective alternatives exceeded the harm that could be caused by exposing those patients to drugs with unknown side effects.

More broadly, it might be the case that the collective good that helpful drugs do substantially exceeds the collective harm inflicted by unsafe drugs that make it to market and may have been hurried there. For instance, one study (Philipson et al. 2008) found that acceleration of the FDA’s review of new drug applications facilitated by user fees created by the 1992 Prescription Drug User Fee Act (PDUFA) found that the benefits of added speed outweighed costs by a substantial margin—even if all harms caused by drugs approved after the law was passed were blamed on the legislation. The authors write that the benefits of added speed, even after such an assumption was made, outweighed costs by at least three to one. The authors suggest that “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.”

Every drug presents its own unique regulatory challenges, of course, and it is impossible to predict benefits or risks with complete confidence. But by expanding the FDA’s resources to review new drug applications, one of the steps pursued under the PDUFA, the agency was able to substantially reduce the backlog of drugs awaiting regulatory review without
any impact on either the rate of drug withdrawals or the time it took to withdraw them. Another reason to favor the expedition of reviews and approvals is that drugs producing unacceptable numbers of serious side effects among the public at large are likely to be quickly discovered and withdrawn, while a beneficial drug does good for years and years, or at least until such time as an even better drug supersedes it.

Additional FDA reforms, coming under the general heading of “accelerated approval,” reflected a willingness to approve new drugs earlier in the drug-development process, on the strength of “surrogate” markers suggesting that they were “reasonably likely … to predict clinical benefit.” Under these standards, a drug that was likely to be effective against a given disease could be given provisional approval before the completion of final-stage clinical trials and review of the resulting data, as is the FDA’s customary process.

Despite these reforms, the FDA still lacks a transparent mechanism for quantifying the gains in patients’ health that are likely to result from faster approvals, for measuring the offsetting costs of potential side effects, and for comparing the two and deciding on that basis whether and to what extent the regulatory process should be streamlined. Put another way, a complete view of the drug-development process would account not only for drug companies’ direct costs but for the benefits that producers and consumers are deprived of.

This paper reexamines the costs of the drug-development process in this light and illustrates empirically how incorporating what economists refer to as producer and consumer surplus into the social cost of R&D affects our understanding of the cost of delays. Since recognition of these values is now absent from the FDA’s determination of how extensive and fast-moving the regulatory process should be, the result of such an evaluation should be to expedite the approval of novel therapies promising important therapeutic benefits to the public at large. These invariably provide concomitant economic benefits to the producer responsible, in the form of increased profits, which may be used to underwrite additional innovation.

It bears noting that the benefits of an exhaustive review process are far less extensive than is generally supposed. Even especially large, lengthy, and expensive clinical trials will involve only a small fraction of the numbers of patients who will ultimately ingest an approved drug. And the trial cohort may be younger, healthier, or in other ways markedly different from those members of the public at large who take the drugs in question on doctor’s orders. Also, doctors may prescribe these drugs for ailments other than the ones for which they were invented and evaluated, further complicating the question of how effective trials are in exposing side effects that the public will be asked to tolerate.

In short, premarket testing may reveal relatively little about a product’s safety and efficacy for the potential millions of nonparticipants in trials who ultimately try it. Because the problems associated with many drugs, such as Vioxx, an anti-inflammatory linked to cardiovascular incidents, are subtler than, say, those caused by thalidomide, a new set of tools (including a more intensive system of post-market surveillance) may be better than premarket testing at promoting safety, while permitting effective drugs to reach more quickly all those who might benefit from them.

It goes without saying that innovations such as biomarkers and sophisticated statistical analysis, which might discover a broad range of effects at earlier stages of clinical trials, which wouldn’t therefore need to be as large or as extended, should be developed and implemented. Biomarkers are by-products of disease processes (such as decreased numbers of CD4 cells in AIDS cases) or indicators of disease risk (such as cholesterol levels for heart disease) that allow researchers to predict the likelihood of success of treatments without having to wait for the completion of full clinical trials.

Under enhanced post-market surveillance, rapid feedback mechanisms would be in place through which medical practitioners and patients could report on the benefits and side effects of new treatments they either administer or undergo. In the case of severe rheumatoid arthritis, for example, the FDA would then be in a position to balance the
added cardiovascular risks posed by COX-2 inhibitors against the pain relief that such drugs offer sufferers.

On the basis of evidence that acceleration of the drug-development and approval process does, in fact, offer substantial benefits to patients, we conclude that the FDA should take steps to speed drug development that do not pose an undue hazard to public health and safety.

**THE VALUE OF SPEEDIER REVIEW**

Here we summarize more elaborate recent research (Philipson and Sun et al. under review) that explicitly quantifies the social benefits of a streamlined approval process in the case of three treatments: HAART, for HIV/AIDS; rituximab (Rituxan), for non-Hodgkin’s lymphoma; and trastuzumab (Herceptin), for breast cancer.

Our main empirical finding is that the social costs of delays in drug development, as measured by changes in consumer surplus and profits, far outweigh the traditional measure of R&D costs discussed above. The analysis applies to a greater number of drugs than the three studied, but we chose those three because they highlight the dramatic impact that new pharmaceuticals can have on well-known, serious, and even fatal diseases, and therefore what the social returns of a faster approval process for these medicines could have been.

We recognize that many otherwise effective drugs do not produce treatment effects that are as large. However, reduced delays in public access to drugs embodying incremental innovations are also likely to generate a very large consumer surplus if they treat large patient populations or introduce therapeutic options to physicians and patients that had not been previously available. Even new drugs that are not curative may offer very significant benefits if they improve sufferers’ productivity (in the form of lower absenteeism, for instance) by alleviating disabling symptoms.

Our results for the three drugs we reviewed show the following:

- **The sale of these drugs benefited patients far more than they did the pharmaceutical firms that developed them.** We estimate that HAART was worth $330 billion to AIDS patients; rituximab, $8 billion to lymphoma patients; and trastuzumab, $137 billion to patients with breast cancer. Profits to firms were small in comparison: $27 billion for HAART, $3 billion for rituximab, and $9 billion for trastuzumab.

- **A development process that allowed these three drugs to enter the market one year earlier would have provided enormous social benefits, particularly to patients.** Earlier entry by one year would have increased the benefit of HAART to patients by $19 billion (a 6 percent increase); $310 million in the case of rituximab (4 percent); and $8 billion in the case of trastuzumab (6 percent). Profits of the firm marketing HAART would have increased by $4 billion (14 percent); $260 million for the firm marketing rituximab (8 percent); and $730 million for the firm marketing trastuzumab (8 percent).

- **A process that accelerated entry of these drugs by three years would have had even more dramatic effects, raising the benefit by $53 billion (16 percent) for patients who took HAART; $850 million (11 percent) for those who took rituximab; and $22 billion (15 percent) for those who took trastuzumab.** Profits from HAART would have increased by $12 billion (44 percent); $750 million (24 percent) from rituximab; and $2 billion (23 percent) from trastuzumab.

- **A streamlined process would have comparatively little effect on firms’ R&D costs.** We find that a reduction in the amount of time a drug spends in Phase III clinical trials or awaiting FDA approval would affect average R&D costs of all drugs by, at most, $40 million each.

Overall, our results suggest that in the case of these three drugs, a streamlined approval process would have generated significant social returns, particularly for patients, and that current measures of the R&D implications of drug lags are misleading. Thus, efforts...
to streamline the drug-development process that minimize any reduction in safety should be of great social value.

Although it is beyond the scope of this paper to elaborate on specific reforms that could be tried, we would suggest that policymakers consider additional research into and evaluation of the following:

- Speeding recruitment into clinical trials, by, for example, allowing stipends to be paid to volunteer participants. On ethical grounds, such payments are not now permitted. Since forms of permissible employment—for example, construction work—do pose safety hazards, it is not clear why clinical trials in which participants are informed of the risks should merit special treatment, especially in view of the benefits that such participation could bring to the public at large.

- Adopting technologies such as biomarkers that might allow clinical trials to be conducted more expeditiously.

- Continuing to streamline the clinical-trial review process, by, for example, offering FDA regulators performance incentives under the Prescription Drug User Fee Act to adopt techniques that could more rapidly identify promising new treatments or to evaluate new clinical-trial guidelines. Additional funding could also be used to expand the number of reviewers.

- Establishing an ombudsman to review the impact of FDA regulations and practices on drug-development times. As explained above, the FDA’s natural inclination is to be overly cautious in approving drugs for public distribution. An ombudsman could restrain this tendency.

- Establishing permanent funding of the Reagan-Udall Foundation. Created but not funded by PDUFA’s 2007 reauthorization, the foundation is charged with modernizing the drug-development process in consultation with the FDA.

The remainder of this report is organized as follows. We begin with an overview of the drug-development process, including a discussion of the timelines and costs involved. We then discuss our research quantifying the social returns of a streamlined development process, and conclude with a discussion of the implications and limitations of our findings, as well as some policy recommendations.

**THE DRUG-DEVELOPMENT PROCESS, TIMELINES, AND COSTS**

Drug development proceeds through several stages. In the first stage, preclinical toxicology trials, the firm identifies and studies a particular agent of interest by looking at chemical evidence, animal studies, foreign experience, use of the drug for treating other conditions, and the like. If these results are promising, the firm then enters the FDA approval process, consisting of three phases of clinical trials. Phase I trials seek to evaluate a drug’s safety and to obtain data on its pharmacological properties. Typically, these trials enroll small numbers (twenty to eighty) of healthy volunteers. Phase II testing enrolls slightly larger numbers (100–130) of sick volunteers for the purpose of investigating a drug’s efficacy and determining its optimal dosage, as well as monitoring the drug’s safety in diseased patients. Phase III testing typically involves still-larger numbers of sick patients (more than 1,000) and is the most costly stage of the approval process. Phase III testing seeks to establish more definitively the efficacy of a drug, as well as to discover any rare side effects. Upon completion of Phase III testing, the firm submits a New Drug Application to the FDA, which is accompanied by the results of the clinical trials. The FDA may then reject the application, require further clinical testing, or approve the drug outright.

Following approval, a drug enters post-market surveillance, also known as Phase IV testing. During it, manufacturers conduct additional studies that the FDA may require for the sake of assessing long-term safety. In addition, drug firms, physicians, and patients can report any suspected adverse reactions to the Medwatch/Adverse Event Reporting System.
(AERS), which is monitored by the FDA. The agency can then choose to withdraw its approval if it believes the drug to be unsafe.

Table 1 outlines the costs and timelines involved at each stage of the drug-development process, according to studies by DiMasi, Hansen, and Grabowski, who estimate these timelines and costs using proprietary R&D data from a sample of U.S. firms (DiMasi et al. 2003). The table shows the duration of each stage as well as its annual costs. For example, the authors find that Phase III trials typically last 2.8 years at a cost of $56 million per year. Given these annual costs, the authors then proceed to calculate the lifetime present value of R&D costs at the time of marketing. This lifetime value, $1 billion, incorporates the lost interest (or opportunity costs) of drug R&D and is essentially the net present value of R&D costs, carried forward to the time of marketing at an 11 percent interest rate.

**Table 1. Stage-Specific and Lifetime Costs of R&D and Drug Approval**

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<thead>
<tr>
<th>PREMARKETING STAGE</th>
<th>LENGTH OF TIME (YEARS)</th>
<th>COST PER YEAR ($, MILLIONS)</th>
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<tbody>
<tr>
<td>Preclinical</td>
<td>4.3</td>
<td>33.0</td>
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<tr>
<td>Phase I</td>
<td>1.1</td>
<td>86.3</td>
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<tr>
<td>Phase II</td>
<td>2.1</td>
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<td>Approval phase</td>
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<td>Lifetime net present value cost at time of marketing</td>
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Notes: All values shown are in 2008 U.S. dollars. The lifetime net present value cost reflects an 11 percent discount rate. Source: Authors’ calculations based on data reported by DiMasi et al. 2003

**The Social Effects of a Speedier Drug-Development Process**

*Given the current costs and timelines of the drug-development process, as discussed above, we performed an analysis to determine how a streamlined process might benefit patients.*

We consider several diseases in our analysis: AIDS, non-Hodgkin’s lymphoma (NHL), and breast cancer. In the case of AIDS, we estimate the impact on survival of the introduction, in 1997, of highly active antiretroviral therapy (HAART). For NHL, we estimate the impact on survival of the novel monoclonal antibody rituximab (Rituxan), introduced in 1998. Finally, we estimate the impact on survival of trastuzumab (Herceptin), a monoclonal antibody introduced in 1999 and designed for the treatment of Her2-positive breast cancer. In the case of these diseases, recent therapeutic improvements have notably improved survival rates. For example, in the absence of treatment, AIDS is rapidly fatal, with nearly 50 percent of patients dying in the first year of the disease. However, our results suggest that HAART increased life expectancy for AIDS patients by nearly fourteen years. Therefore, a process that hastened HAART’s entry by even a year would have been of enormous value to patients.

Our approach to estimating the value of early entry is based on a patient’s “willingness to pay” (WTP) for the treatment in question (Figure 1). Consider a patient whose disease begins in a particular year and who receives a certain amount of income every year he is alive. We then ask: How much would the patient be willing to pay annually for every year the treatment keeps him alive? Figure 1 shows the case of a patient with AIDS. We begin our calculation by determining the amount of money (X in Figure 1) that the patient would be willing to pay to have obtained access to HAART in 1997, the year it became available. We then determine how much the patient would be willing to pay to have gained access to HAART in 1996 (Z in Figure 1). The value of HAART’s entering the market...
a year earlier is therefore the WTP for the drug in 1996 minus the WTP for the drug in 1997 (Figure 1). Similarly, the value of HAART’s entering the market three years earlier would be the WTP for the drug in 1994 minus the WTP for the drug in 1997.

We used an economic model to estimate a patient’s WTP to obtain access to drugs in a given year. This model has been used for this purpose in many other contexts (Lakdawalla et al. forthcoming, Philipson and Jena 2006, Becker et al. 2006), and the technical details of this model can be found in our study (Philipson and Sun et al. under review). As suggested by Figure 1, our model implies an influence by the following factors on a patient’s WTP:

- **The survival benefit conferred by a given drug.** As shown in Figure 1, WTP simply represents a trade-off: How much income is a patient willing to give up in order to obtain access to a drug? Clearly, the larger the survival benefit conferred by a given drug, the more the patient will be willing to pay.

- **The patient’s income.** Since the amount of income a patient is willing to give up in order to obtain a drug will reflect how much income he has, the amount in question will generally increase as income increases.

- **The year in which the patient’s disease begins.** The year in which the patient’s disease begins will have two effects on WTP. First, a patient’s longevity—or, more precisely, the drug’s effectiveness in extending life—will depend on how long the patient has had the disease before the drug became available and he took it for the first time. Second, the length of the period of illness preceding the drug’s availability will affect a patient’s willingness to pay for the drug. Consequently, patients who were first diagnosed with AIDS/HIV infection in 1997 would not have been willing to pay anything at all to obtain HAART earlier than 1997, since a patient’s ingestion of a drug before the disease that it was designed to treat had been diagnosed would be of no value in extending the patient’s life.

The discussion above suggests that in order to calculate WTP, we need to populate our model with estimates of survival of each disease, the effect of each drug on survival, and estimates of patient income. For non-Hodgkin’s lymphoma and breast cancer, we obtained from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database longitudinal survival data for persons diagnosed between 1984 and 2000. For AIDS, we used survival data reported by Philipson and Jena (2006), who estimate survival curves for AIDS by year of diagnosis using data from the U.S. Centers for Disease Control. With these survival data in hand, we then used regression analyses to estimate how the entry of each drug affected disease survival. Finally, we assume an annual income of $69,200, which is
twice the GDP per capita in 2000, and reflects the value of earned income and leisure.\(^6\)

Finally, note that WTP represents the gross value to the patient of access to a drug in a particular year. The net benefit to patients is this gross value minus the cost of the drug itself. The medical literature suggests that the estimated annual cost of HAART is $10,000-$15,000 (Chen et al. 2006), so we used $15,000 as a baseline estimate for the annual cost of the drug. In the case of rituximab and trastuzumab, we used a large database of administrative health claims to estimate average annual spending for each drug, and found average annual spending of $506 for trastuzumab and $1,212 for rituximab.\(^7\)

**Results**

Our analysis examined the social benefits of earlier drug adoption for patients whose disease was diagnosed between 1984 and 2000. Table 2 shows the average net benefits to patients of earlier drug adoption for each of the drugs we considered, which is simply the WTP to obtain the drug in a given year minus spending on the drug, averaged over each cohort of patients in that period. The row “Baseline Value” represents the average WTP for the drug in the year that it actually entered the market (1997 for HAART, 1998 for rituximab, and 1999 for trastuzumab), while the remaining rows show patients’ WTP for earlier entry dates for the drug. The table makes two key points: first, each of the drugs was highly valued by patients for its large effect on survival. For example, we find that AIDS patients were willing to have paid nearly $290,000 out of their lifetime income for access to HAART in 1997. Second, our results show that earlier entry is highly valued by patients: they would have been willing to pay roughly an additional $16,000 for access to HAART in 1996 and over $46,000 extra for access to HAART in 1994. These large sums reflect the power of earlier access to extend the life span of those with diseases that kill relatively quickly.

Table 3 plots the aggregate social returns for each drug, which are simply the individual amounts shown in Table 2 multiplied by the number of patients, as well as our estimates of pharmaceutical firms’ profits. As with Table 3, “Baseline Value” is the value of the drug (for patients and firms) in the year that it entered

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<th>Table 2. Average Benefits to Patients from Earlier Drug Adoption</th>
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<td>Baseline Value</td>
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<td>2 years earlier</td>
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<td>3 years earlier</td>
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</table>

Notes: Values shown are in 2008 dollars. Source: Authors’ calculations.
the market, with subsequent rows showing changes in value resulting from earlier entry dates. In the case of AIDS, we estimate that the introduction of HAART in 1997 offered benefits to patients worth $330 billion and earned roughly $27 billion in profits for the firms marketing the drugs. The large benefit for patients, more than ten times the benefit for firms, is not surprising in light of HAART’s success at dramatically extending survival. Earlier entry by one and three years would have conferred additional benefits to patients of $19 billion (a 6 percent increase) and $53 billion (a 16 percent increase), respectively. Earlier entry by one year would have raised firms’ profits by almost $4 billion (14 percent); earlier entry by three years would have raised profits by $12 billion (44 percent).

In sum, increases in firms’ profits would have been lower than increases in consumer surplus in absolute terms ($4 billion vs. $19 billion and $12 billion vs. $53 billion), though higher in relative terms (14 percent vs. 6 percent and 44 percent vs. 16 percent).

The entry of rituximab in 1998 offered benefits to patients worth roughly $8 billion and to firms $3 billion, with these smaller numbers reflecting both the lower incidence of NHL and rituximab’s smaller impact on longevity. Earlier entry by one year would have been worth an additional $310 million (4 percent) to patients and an additional $260 million (8 percent) to firms, while earlier entry by three years would have been worth an additional $850 million (11 percent) to patients and $750 million (24 percent) to firms. The introduction of trastuzumab in 1999 was valued at $137 billion by patients and generated $9 billion in profits for firms. Earlier entry by one year would have augmented the benefit to patients by $8 billion (6 percent) and added an additional $730 million (8 percent) to profits. Had trastuzumab entered the market three years earlier, patients would have gained an additional $22 billion in value (15 percent), and firms would have earned an additional $2 billion (23 percent).

By contrast, we show in Table 4 how reducing the amount of time a drug spends in either Phase III clinical trials or in the FDA review process would affect R&D costs. Compared with the values shown in Table 3, which are measured in the billions of dollars, the effect on R&D costs is quite small. We estimate that shortening Phase III by one year would reduce R&D costs by only about $40 million on average per firm.

In sum, our analysis suggests that earlier introduction of these three drugs would have produced substantial social returns for patients and firms, with patients generally receiving the larger share of benefits. To put it differently, patients would have benefited from earlier access to these drugs to a much greater degree than firms would have benefited in the form of increased profits. Moreover, we find that the benefits that patients receive from earlier drug entry dwarf any reduction in pharmaceutical firms’ R&D costs. Clearly, shortening development times would be no giveaway to producers.

CONCLUDING REMARKS AND POLICY RECOMMENDATIONS

Our empirical analysis of three drugs (HAART, rituximab, and trastuzumab) suggests that determining the value to patients of earlier
access to beneficial therapies provides a more precise understanding than has been previously available of the benefits of a streamlined drug-development process—and the costs of delays. In particular, we find that the social costs of lost profits as well as lost consumer surplus vastly exceed the additional costs that a lengthened R&D and drug-approval process may entail, indicating that delays are costlier to patients than producers.

Our analysis has several limitations that future work may want to overcome. We focused our analysis on three drugs now known to have significant health benefits. Therefore, it is reasonable to ask to what extent our results apply to other drugs. Given that most FDA-approved drugs offer no more than incremental improvements over existing treatments, the social surplus provided by accelerated access to such medicines may be more modest. However, our model suggests that patients would still benefit from timelier access; in aggregate, the resulting gains are likely to be quite large.

It is worth noting that we considered the effect of drugs on only the length of life. Estimates of the value of timelier access to drugs that improve the quality of life would produce different figures. New drugs for chronic ailments such as hypertension, hypercholesteremia (high cholesterol), or diabetes, for example, may not produce the dramatic improvements of the three drugs we studied. However, large cohorts suffer from these ailments, and the larger the patient population taking a drug, the larger the social impact of its availability. It also bears noting that in the case of rituximab, we considered only its benefits to patients with non-Hodgkin’s lymphoma. Since the drug is effective against other diseases, such as rheumatoid arthritis, our estimates understate the social benefits of earlier adoption.

The most significant limitation of our study may be that we focused only on drug benefits rather than side effects. Thus, a crucial question is whether a streamlined development or approval process would lead to an increase in the number of unsafe drugs entering the market. However, evidence concerning the impact of PDUFA suggests that, at least in recent years, the benefits of a streamlined approval process, under even the most conservative assumptions, have significantly outweighed any reductions in drug safety.

Moreover, as we suggest in our introduction, there are ways to streamline the development process that need not detract from drug safety. For example, difficulties in recruiting patients to join clinical trials (Frantz 2003) may be overcome by paying stipends to those who are eligible. Standard screening and other safety protocols would still be preserved. Accelerated trials would be followed by enhanced post-market surveillance, which might be more effective than premarket scrutiny of a trial’s cohort in detecting rare side effects, given the much larger number of patients to whom a drug would be marketed.

Our analysis also neglects an important benefit to firms of a streamlined approval process—the stronger incentives to innovate that the promise

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Lifetime Net Present Value Cost of R&amp;D and Approval ($, Millions)</th>
<th>Change in Lifetime Costs ($, Millions)</th>
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<tr>
<td>Status quo</td>
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<tr>
<td>1 yr. improvement</td>
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<tr>
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<tr>
<td>Approval</td>
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<tr>
<td>Phase III and approval</td>
<td>369</td>
<td>-42</td>
</tr>
</tbody>
</table>

Notes: All values shown are in 2008 dollars.
Source: Authors’ calculations based on data reported by DiMasi et al. (2003). The lifetime net present value cost of R&D and approval is decided at the initiation of the preclinical phase. The status quo estimate represents the current lifetime cost of R&D and drug approval. This is compared with the estimated cost of a single year’s delay (improvement) in either the length of Phase III or the length of the approval period, or both.
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of increased profits would provide, as well as the greater resources to do so that the actual resulting profits would provide. Indeed, Olson (2009) finds that the abbreviation of drug-review times that PDUFA accomplished was followed by an increase in the number of drug launches in the U.S. market. Our findings suggest that efforts to improve the speed of drug development could generate tremendous social returns. Steps worth considering include:

- **Allowing the payment of stipends to clinical-trial volunteers.** Facilitation of recruitment by such measures would help clear the present bottlenecks, while having a minimal effect on the safety of participants.

- **Adopting technologies such as biomarkers, which offer the potential to accelerate clinical trials.** These would have special value in the case of diseases such as multiple sclerosis that progress slowly to clinical endpoints such as disability. To ensure no reduction in safety, the FDA could require trials employing biomarkers to meet a higher evidentiary standard.

- **Strengthening the Prescription Drug User Fee Act (PDUFA).** After an initial improvement in FDA processing rates resulting from the hiring of additional staff, review times stagnated. A new influx of reviewers could shorten development times further.

- **Establishing an ombudsman.** Such an office could review the effects of FDA regulations and practices on the speed of drug development.

- **Strengthening the financial position and authority of the Reagan-Udall Foundation.** That independent body is charged with setting up projects and programs that assist the FDA in modernizing the drug-development process while continuing to serve its obligations to the public.

Despite many controversies over the FDA’s efforts to ensure drug safety and efficacy, there has been little empirical examination of the cost to patients, as opposed to companies, of delays in drug development. We demonstrate the importance of quantifying the cost of delay for every drug under development and the benefits of acceleration in the case of three selected drugs. These findings should be a basis for reforming the process of reviewing drugs developed for ultimate distribution to the public.


1. Both income and health grew by 2 percent annually. The authors use an economic model to estimate the subjective economic value to consumers of increases in longevity.

2. HIV is a virus that attacks cells known as CD4 T cells, which are crucial to the functioning of the immune system. AIDS is a disease caused when HIV has caused sufficient damage to the immune system that the number of CD4 cells falls below a defined level (200/µl) or the patient begins to suffer from several characteristic infections.

3. The regulations for Subpart H read in part: “FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.” A full description of the Subpart H regulations is available online at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm121606.htm.

4. For a more detailed overview of the drug-approval process, see Philipson and Sun 2008.

5. AIDS presents an interesting case because the highly active antiretroviral treatment (HAART), which greatly improved survival, consisted of three drugs, which entered the market at different times: nucleoside analog reverse transcriptase inhibitors (NRTIs) in 1988, protease inhibitors (PIs) in 1996, and non-nucleoside analog reverse transcriptase inhibitors (NNRTIs) in 1997. Since HAART is a combination of all three drugs and the NRTIs were far less effective than the later PIs and NNRTIs, we used the latest year of entry (1997) to mark the entry of HAART.

6. U.S. GDP per capita in 2000 was $34,600, which reflects the average value of consumption (of goods and services) per patient. However, since the benefit of living an additional year reflects the value of leisure time in addition to the value of consumption, economists typically speak of full income, which reflects the value of both. Following methods employed elsewhere (Murphy and Topel 2006), we assume that full income is equal to twice earned income.

7. These numbers may seem small—for example, mayoclinic.com reports the average cost of trastuzumab at $36,000–$65,000 per year. However, while HAART is indicated for nearly all AIDS patients, neither trastuzumab nor rituximab is indicated for all breast cancer and NHL patients, respectively. Our estimated figures are the average spending among all breast cancer and NHL patients; they indicate the number of recipients to be small.

8. For example, see Lichtenberg 2010 for a broad discussion of the impact of newer pharmaceuticals on cancer mortality.
The time and costs required to bring new medical products to market is growing ever larger. Today, it may take more than a decade, and hundreds of millions of dollars, to bring a single medical innovation to the public from initial conception to FDA approval. The slow pace and high cost of development contributes to the cost of health care and delays patient access to potentially lifesaving products.

At the same time, the FDA is facing a crisis in confidence among consumers, media and policymakers, with some critics declaring the agency “broken”—unable to ensure that medical products offered for sale in the U.S. are reasonably safe and effective. Doctors and academic medical centers, too, face growing concerns about allegedly harmful interactions with industry during the development and marketing of medical products. The result is a growing call for sweeping new regulation of the industry at both the state and federal levels.

Advances in the molecular and genetic understanding of disease have the potential to make health care more predictive and preventive rather than empirical and reactive—thus improving patient outcomes and reducing health-care costs. Unfortunately, in our zeal to reduce risks, regulate potential conflicts, and mandate transparency, we may reduce incentives for companies to develop and market improved products due to increased tort litigation; inhibit doctors from collaborating with companies in designing safer and more effective products; and slow the FDA’s efforts to bring its oversight activities into conformity with the latest scientific and technical advances.

The membership of Project FDA includes practicing physicians, scientists, economists, medical ethicists, and policy experts. Committee members will examine the current framework and direction of federal and state regulation to ensure that the medical innovation pipeline remains robust and that all stakeholders—including industry, academic medical centers, and regulators—are taking advantage of appropriate opportunities to bring safer and more effective products to market utilizing 21st Century technologies.

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