

Philipson, Tomas J.; Sun, Eric

Working Paper

Is the Food and Drug Administration Safe and Effective?

Working Paper, No. 218

Provided in Cooperation with:

George J. Stigler Center for the Study of the Economy and the State, The University of Chicago Booth School of Business

Suggested Citation: Philipson, Tomas J.; Sun, Eric (2007) : Is the Food and Drug Administration Safe and Effective?, Working Paper, No. 218, The University of Chicago, George J. Stigler Center for the Study of the Economy and the State, Chicago, IL

This Version is available at:

<https://hdl.handle.net/10419/262620>

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**“IS THE FOOD AND DRUG ADMINISTRATION
SAFE AND EFFECTIVE?”**

TOMAS PHILIPSON

AND

ERIC SUN

**George J. Stigler Center for the Study
of
the Economy and the State**

The University of Chicago

Is the Food And Drug Administration Safe And Effective?

Tomas J. Philipson and Eric Sun

Tomas J. Philipson is a Professor at The Irving B. Harris Graduate School of Public Policy Studies, University Of Chicago, Chicago, Illinois. Eric Sun is a Fellow in the Bing Center for Health Economics at RAND in Santa Monica, California, as well as the Medical Scientist Training Program at the University of Chicago in Chicago, Illinois. Their e-mail addresses Are <t-philipson@uchicago.edu> and <eric.sun@uchicago.edu >, respectively.

In virtually all developed countries and many undeveloped ones as well, regulatory authorities provide public oversight of the safety and efficacy of many medical products and foods. In the United States, such oversight is conducted by the Food and Drug Administration (FDA), which regulates drugs, medical devices, biologics (products made from living organisms, like vaccines and blood products), cosmetics, radiation-emitting electronic products, veterinary products, and foods. The FDA regulates all food products except meat and poultry, which are regulated by the United States Department of Agriculture, although the FDA regulates game meats. According to the FDA, the products it regulates account for more than one-fifth of U.S. consumer spending. In the area of medical products, the agency is responsible for determining whether marketed products are both safe and effective before and after they have been marketed.

Compared to many other regulatory agencies, relatively little research has been done by economists on the efficiency tradeoffs involved with the FDA, although existing analyses include Peltzman (1973) Grabowski, Vernon, and Thomas (1978), Wiggins (1981), and Schwartzman (1976). It is somewhat ironic to conjecture that if a product application was supplied to the FDA with the scant amount of analysis or evidence that currently exists on the efficiency or performance of the policies of the agency itself, such an application would clearly be rejected on the basis of insufficient analysis or evidence. In this paper we discuss and summarize in a non-technical manner recent research on the FDA that sheds new light on whether the policies of the agency itself are safe and effective. Although the discussion is specific to the FDA, some of this research could potentially apply to other areas of regulation as well, such as e.g. transportation.

We begin with some background on the statutes and regulations that govern the Food and Drug Administration. We then stress two static and dynamic issues that seem fundamental to the efficiency of the FDA. The static issue concerns the potential inefficiency of the duality of product safety laws when such functions are performed not only by the FDA but also by the private sector in a complimentary way through product liability law. Put another way, what is the rationale for using product liability *and* the FDA to regulate drug safety? While intuitively it may seem that two systems must be better than one in ensuring drug safety, it is important to remember that each system comes with costs, so patients can be harmed by the inefficient duplication. When product liability law attempts to ensure safety already assured by the FDA, prices may be inefficiently high due to liability costs that do not deter manufacturers from producing unsafe products. Due to this duplication inefficiency, we will argue that the benefits of a product liability exemption for products that have passed through FDA approval could be potentially large.

We then turn to the dynamic issue, which concerns the extent to which higher safety is achieved at a cost of later market entry of effective and even life-saving products. After considering the general tradeoffs involved, we discuss the Prescription Drug User Fee Acts (PDUFA), which raised the speed of the agency's regulatory process starting in 1992, although according to some, at the cost of reducing drug safety. We discuss recent work that argues that the increased speed offered greater benefits than the corresponding decrease in safety. We conclude by suggesting a research agenda for future work on the Food and Drug Administration.

Background on the Regulation and Liability of Medical Products

Regulation of Medical Products through the FDA

The Food and Drug Administration (FDA) is an executive-branch agency that is led by a Commissioner who is appointed by the president, with Senate confirmation, and who reports to the Secretary of Health and Human Services. The current commissioner is Andrew von Eschenbach, a doctor who before coming to the FDA in 2006 ran the National Cancer Institute for four years. The Commissioner oversees an agency with 9,000 employees and a current budget of roughly \$2 billion. Generally, speaking, the role of the FDA is to ensure the safety and accurate labeling of the products that it regulates. With respect to drugs, biologics, and medical devices, the FDA is additionally charged with ensuring the efficacy of these products.

The FDA's statutory authority comes from the Federal Food, Drug, and Cosmetics Act (FDCA), which was passed in 1938 in response to public outcry over deaths from the drug Elixir Sulfanilamide, a drug used to treat streptococcal infections. While Elixir Sulfanilamide was safe in tablet and powder forms, in 1937 the S.E. Massengill Co. released a liquid form which contained a lethal solvent in its preparation. As a result, over 100 people died, including many children. The FDCA mandated regulatory approval of new drugs before they could be sold. Before marketing a drug, firms were required to submit a New Drug Application to the FDA establishing the safety of their products. If the FDA was not convinced of a drug's safety, then it had 180 days from the receipt of the application to block the drug's introduction into the market. In addition, the law required that new drugs be accompanied by appropriate labeling for safe use. The FDA used this latter requirement to introduce the notion of prescription drugs, as it ruled that some drugs could not be safely used without a physician's prescription. The distinction between over the counter and prescription drugs was formalized by the Durham-Humphrey Amendment of 1951.

The 1962 Kefauver amendments to the FDCA notably strengthened the agency's regulatory power. First, the amendments removed the 180 day time limit, so now no drug could enter the market unless the FDA gave its explicit approval. Second, the Kefauver amendments required drug manufacturers to prove the safety *and* efficacy of a drug prior to marketing. Finally, the Kefauver amendments gave the FDA control over the drug testing process itself. Now, manufacturers were required to submit their drug testing plans to the FDA, and the agency had the right to mandate changes in a firm's testing plan.

The Prescription Drug User Fee Act of 1992 was the next major piece of legislation affecting the drug approval process. It allowed to the FDA to levy user fees from firms filing a New Drug Application or Biologic License Application, in exchange for guarantees on review times. This legislation was subsequently renewed as part of the Food and Drug Modernization Act of 1997, and then again as part of the Public Health and Bioterrorism Preparedness Act in 2002. The guarantee on review time is not a guarantee of approval; rather, it is a guarantee that the FDA will take action on (most) applications within a specified period of time. In particular, within the specified period, the FDA must issue one of three possible actions: 1) a "non-approvable" letter indicating that the application has not satisfied the FDA's standards for safety and/or efficacy; 2) an "approvable" letter that indicates the application can be approved if certain deficiencies and questions are acted upon by the sponsor; 3) an ultimate approval letter that gives the sponsor company the right to market the drug to the public. Submissions for new drugs or biologics are assigned either a "standard" or "priority" status, depending in part on their novelty and on the existence of unmet needs. The FDA is required to deliver a "complete review" on 90 percent of priority applications within six months. For standard applications, the FDA was

obliged to review 90 percent of applications in twelve months under the 1992 law; currently, the FDA is mandated to review 90 percent of standard applications within ten months.

The user fees levied by the Prescription Drug User Fee Act of 1992 and its continuing legislation can be quite substantial. In the initial fiscal year 1993 user fee schedule (all costs shown here are in 2007 dollars), applications with clinical data were assessed a one-time fee of \$141,000; each supplemental application with clinical data, and applications with no clinical data, \$70,414; annual manufacturing establishment fees were \$58,011, and annual product fees were \$8,449. By fiscal year 2004, applications with clinical data were assessed a one-time fee of \$617,822 (a 338 percent increase since 1992) ; each supplemental application with clinical data, and applications with no clinical data, were assessed a user fee of \$308,911 (338 percent increase); annual manufacturing establishment fees were \$244,328 (321 percent increase), and annual product fees were \$6,463 (7 percent increase).¹

Figure 1 presents an overview of the U.S. drug development process. In the first stage, preclinical toxicology trials, the FDA has not yet entered the picture, but the firm is studying and testing the properties of a potential new drug by looking at chemical evidence, animal studies, foreign experience, use of the drug for treating other conditions, and the like. The government drug approval process begins when a firm files an Investigational New Drug application, which requests permission from the FDA to conduct clinical trials on humans. Typically, this application contains the available preclinical information, as well as protocols for the drug's clinical trials.

¹ Waivers and exemptions are granted to small firms, and to sponsors submitting an application under the Orphan Drug Act of 1983. U.S. Food and Drug Administration [2004], "Prescription Drug User Fees—Overview", *U.S. Food and Drug Administration* [online] (cited 27 April 2004), at <<http://www.fda.gov/oc/pdufa/overview.html>>.

Once the FDA gives its approval, the firm may begin conducting clinical trials for the drug, which proceed in three phases. Phase I trials seek to evaluate a drug's safety and to obtain data on a drug's pharmacologic properties. Typically, these trials enroll small numbers (20-80) of healthy volunteers. Phase II testing then enrolls slightly larger (100-130) numbers of sick volunteers, seeking to begin investigating a drug's efficacy and optimal dosage, and to monitor the drug's safety in diseased patients. Finally, Phase III testing typically involves larger numbers (more than 1,000) of sick patients 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 the 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.

In addition to issuing approval of the drug, the FDA must also approve the label that accompanies it. This label typically provides information on the drug's pharmacologic properties (such as the rate at which the drug enters and exits the body), contraindications (medical conditions that preclude use of the drug) and side effects, as well as brief summaries of the clinical trials reported to the FDA. Perhaps most importantly, the label also lists the indications (or diseases) that the drug is approved to treat. Thus, approval by the FDA is not merely approval of the drug, it is approval of the drug for specific uses. If a firm wishes to obtain approval for additional indications, it typically must begin a new set of clinical trials for those indications. Use of a drug for an indication not listed on the label ("off-label use") is not illegal, and indeed occurs regularly in many areas, such as oncology. However, it is illegal for a manufacturer to advertise a drug for a non-approved indication. In addition, insurers may not always pay for off-label use of a drug.

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

Figure 1 provides the average cost and length of time for each phase of clinical testing (Dimasi et al., 2003). In addition, the percentages near the bottom of the figure provide the conditional and unconditional probabilities of success at each stage of the development process. Notice that that later stages of clinical testing become progressively longer and more expensive, especially in Phase III. Overall, the drug development process is extremely time consuming, as the clinical and approval phases combined can take 6.6 to 13 years. In addition, the process has a low probability of success: only 8 percent of drugs for which an Investigational New Drug application is filed ultimately receive FDA approval. Most of this attrition occurs early on in the process. Only 40 percent of drugs for which an Investigational New Drug application is filed progress to Phase I testing, while 90 percent of drugs for which a New Drug Application is submitted after Phase III receive approval. Also, most of the drug approval process is taken up by the clinical testing required prior to submission of the New Drug Application, as opposed to the review process of that evidence by FDA itself. This pattern suggests that the FDA favors safety over speed, as the drug approval process is rather lengthy. The drugs the agency approves tend to be quite safe, in the sense that the agency or private firms seldom withdraw drugs from the market. For example, among the drugs approved by the FDA between 1979 and 2002, only 2.5 percent were late withdrawn from the market (Philipson et al, 2005).

Product Liability for Drugs

While the FDA is the primary and most visible player in drug safety regulation, the product liability system also plays a role in ensuring drug safety by allowing patients to sue manufacturers for unsafe drugs. If a patient experiences an adverse event from a drug, product liability law allows him to sue the firm to recover any damages from the adverse event. Lawsuits over unsafe drugs can generally proceed under one of three theories of legal liability. The first is *defective design*; that is to say, the patient can sue on the basis that the firm designed an inherently unsafe drug. Second, patients can sue for *defective manufacturing* of an otherwise safe drug. Finally, patients can sue for *defective warnings*. In other words, they can sue if they can show that the drug company failed to warn them of the possibility of an adverse event, if it can be established that the firm knew or should have know about that possibility.

Given that the FDA approves both the safety of the drug itself and the sufficiency of the warnings in the drug label, firms have tried to use FDA approval as a shield against product liability suits. Generally speaking, Garber (1993) finds that courts have used FDA approval as a shield for lawsuits over defective design. The reason for doing so stems from a widely cited comment included in *Restatement (Second) of Torts*, which states that drugs are an example of an “unavoidably unsafe product,” in other words, drugs are not generally *unreasonably* dangerous, and the dangers associated with them are not evidence of defects in the drugs themselves. However, for medical devices, rather than drugs, design lawsuits are more common.

The vast majority of drug lawsuits to date have been for manufacturing or failure to warn, and here, courts have in general held that FDA approval of the warnings on the label does not provide a shield against liability lawsuits. With regards to warnings, compliance with FDA

regulations is generally regarded as a minimum standard, so that a firm that does not comply with the FDA is extremely vulnerable to lawsuits. However, compliance with the FDA does not shield a firm against lawsuits. It is important to note that the FDA maintains tight control over the information that a firm can release about a drug, including the release of warnings. For example, the FDA can prohibit the firm from adding a warning to the product label. Even if the FDA prohibits the firm from adding a warning, the firm can still be found liable for failing to warn consumers (Garber, 1993; Calfee, 2006). Lawsuits against firms proceed under state laws, and therefore, the determination of whether the firm knew, or should have known, about a particular risk is based on state-specific legal standards. If the patient prevails at the trial, he can recover compensatory damages for the adverse event, as well as punitive damages, if it is found that the firm intentionally hid evidence from the FDA.

While estimates of the costs of liability for pharmaceuticals are few, there are indications that liability costs are not trivial, especially when viewed as a share of marginal costs. For example, a report prepared by the Council of Economic Advisers (2002) found that in 2000, liability costs across all US industries were \$180 billion, or roughly 1.8 percent of GDP. The same report suggested that the inefficiencies from the liability system were equivalent to the inefficiencies that would occur from a 2 percent increase in consumption taxes, a 3 percent tax on wages, and a 5 percent tax on capital income. In the area of drugs and medical devices, less evidence exists. Manning (1994) identified liability costs for the diphtheria-pertussis-tetanus vaccine by comparing changes in the vaccine's price against changes in the price of the diphtheria-tetanus vaccine. Because the only difference in the vaccines is the pertussis component, which adds a negligible cost to the production price of the vaccine and was the subject of numerous lawsuits, the difference in price between the two vaccines can serve as a

useful estimate of liability costs. Manning's estimates suggest that at their peak, liability accounted for roughly 90% of the price of the diphtheria-pertussis-tetanus vaccine's price. In addition, in related work (Manning, 1997), Manning finds that differences in product liability regimes can explain much of the difference in the Canadian and US prices of drugs. It is important to note that from an economic perspective, what is most important is the fraction of a drug's production costs (excluding fixed costs such as R&D) that are devoted to legal costs. If this fraction is large, then policies that affect firms' legal liability will have larger effects on prices and welfare. Given that the marginal cost of physically producing a drug is generally thought to be low, even if legal costs are also low, they may still account for a significant portion of total production costs.

Static Efficiency and Duplication of Safety Interventions

The first static issue in evaluating a given regulatory regime is to consider how much it affects the safety of the product being provided. In the case of the FDA, this evaluation is complicated by the fact that the safety of medical products is governed both by a regulatory agency and by product liability law. The second dynamic issue is to consider the tradeoff between greater safety and speed to market. Over time the optimal choice of safety or efficacy must balance the gains from increased safety against the losses from delayed introduction of the drug. In the next two sections we will consider these two aspects in turn.

Product Liability and Regulation for Medical Products

In general, one may think of torts as a method to force a potentially negligent party to internalize the full social costs of its actions, since forcing the potentially negligent party to face the expected costs of its harm gives it an incentive to carry out precautionary activities. For

example, in the absence of torts, drivers may not have the proper incentives to avoid accidental harm to pedestrians; torts give drivers a heightened incentive to avoid such accidents. This “Pigouvian tax” interpretation of torts is appropriate for activities that are not taking place in a market context, like automobile accidents, where there are *no prior market transactions* between those potentially inducing harm and those being harmed. However, for the regulation of unsafe products and product liability, the Pigouvian tax interpretation of torts becomes more problematic, because there is a market transaction between the potentially negligent party (the seller) and the buyer. Thus, in addition to analyzing how torts affect the incentives to cause harm, it is also important to consider how torts affect prices and output.

A longstanding literature in economics considers whether and under what circumstances regulation can produce more efficient behavior than liability alone. In effect, this literature bears on the analysis of FDA by seeking to explain why so many governments have sought to regulate the safety of medical products, as opposed to relying on product liability alone. Direct pre-market regulation of safety may be desirable if product liability is in some way incomplete in providing the correct deterrence for producing unsafe products. There are several reasons why product liability may be an incomplete deterrence mechanism in general, and for medical products in particular.

First, product liability will be an incomplete deterrent to the extent that firms can evade judgments against them through limited liability. For example, unsafe medical products can lead to very large losses among consumers, because health and life are valued highly. As a result, firms may be able to avoid judgment by declaring bankruptcy (Shavell, 1987). Moreover, when losses are large, firms have greater incentives to distort the liability system, in a way that makes

that system likely to deter less than it should -- which is one explanation for the change from liability to regulation over time (Glasear and Shleifer, 2003).

Second, with many medical products, it is often difficult to establish whether the firm is at fault, because patients who suffer serious losses from a given drug often have other cofactors which predispose them to injury. As a recent example, Merck, the maker of Vioxx, is being sued by patients because of the increased risk of heart attacks associated with Vioxx usage. However, many patients who used Vioxx often had several other risk factors for heart attacks, therefore making it difficult for the jury to determine whether a given heart attack was caused by Vioxx itself. More generally, if consumers are imperfectly informed, then governments, or a private third party, may economize on the costs of verifying product quality.

Third, new medical products that are the focus of safety and efficacy interventions are provided by firms with patent protection and market power. As argued in Philipson and Sun (2007), in such cases safety may be under provided by a monopolist under product liability for related reasons to under-provision of quality by monopolists more generally Tirole (1998).

Fourth, regulation is a fixed cost for each product, while litigation can involve costs proportional to the number of those potentially harmed, which makes regulation more favorable for larger economies and populations (Mulligan and Shleifer, 2006).

These considerations favor regulation of medical products rather than product liability alone. Nevertheless, most countries have not selected the corner solutions of one regime over the other. Therefore, what needs to be better understood is how these regimes operate in conjunction.

Inefficient Duplication of Safety Interventions

The analysis of medical products policy has generally not focused on the degree to which private or court mechanisms may duplicate the regulatory activities of the FDA (Shavell, 2005; Viscusi, 2005). In Philipson and Sun (2007), we examined the welfare implications of this duplication for the medical products regulated by the FDA. Consider a situation in which a regulatory agency mandates a *binding* level of investment in a given activity, like the intensity of clinical testing, the manufacturing practices the firm must follow, or the extent of warnings about the product, which is higher than what product liability alone would induce for that activity. This binding level may be higher or lower than any efficient level; the key is that it is higher than the level of investment product liability alone would provide, and is therefore binding. Moreover, this level of activity may be costless in the sense of not consuming any resources, as is the potentially the case with the firm's choice of warnings.

Given that the FDA's mandated level of investment is binding, product liability does not have additional deterrence effect beyond the FDA's regulations. However, product liability raises firms' costs and therefore product prices, since it requires firms to pay damages to consumers, and this increase in price for no corresponding gain in product safety reduces social welfare. For example, firms seldom do more clinical testing than what the FDA requires, which suggests that at least for this investment in safety, product liability may sometimes duplicate the role of the FDA. This argument implies a possible rationale for a rule which makes manufacturers exempt from product liability for FDA-regulated activities, such as pre-clinical testing and manufacturing. The argument seems to imply that for drugs, although not devices, the joint safety regulation for design- and manufacturing defects, may be more efficient as FDA is more, though not a complete, safe harbor in those cases. However, for devices in general or liability over failure to warn for drugs, there seems to more of an inefficient duplication.

In Philipson and Sun (2007), we calibrated the potential welfare gains from a product liability exemption for those activities that are regulated by FDA. To illustrate the main argument, suppose that firms' liability costs account for x percent of marginal costs, so that a product liability exemption would eliminate these legal costs and reduce firms' costs by x percent. Together with a given demand structure, such price reductions would imply standard welfare increases. We considered an elasticity of demand for drugs of 1.25 based on our calculations using patent expiration evidence.² This evidence (Grabowski and Vernon, 1992; Berndt, Cockburn, and Griliches, 1996; Caves, 1991), documents supply-induced price changes and the resulting change in quantities demanded. Then, using standard calculations with data on drug sales, we can convert the reduction in marginal costs from liability exemption to reductions in price and gains in welfare (Philipson and Sun, 2007). We used lifetime projected sales data on a sample of 663 drugs that were on the U.S. market between February 1998 and December 2002, with total sales of \$1,149 billion. Details on how lifetime sales data from these drugs was calculated can be found in Philipson et al. (2005).

Figure 2 shows the resulting calibrated welfare gains from a product liability exemption. At the lower end, if liability accounts for 5 percent of a drug's costs, then a product liability exemption would increase consumer welfare by \$47.8 billion (4 percent of sales), producer surplus by \$11.9 billion (1 percent of sales), and total surplus by \$59.7 billion (5 percent of sales). On other hand, suppose that liability accounts for 50% of a drug's costs. In that case, a product liability exemption would increase consumer welfare by \$754.7 billion (66 percent of sales), producer welfare by \$173.9 billion (15 percent of sales), and total welfare by \$928.6

² This elasticity of demand differs from the co-pay elasticity of demand estimated by others (Goldman et al., 2006; Goldman et al., 2007), because the latter is the elasticity of demand from patients who already have insurance, and only need to pay their insurance copay for the drug. Our elasticity of demand is the elasticity of demand facing the manufacturer, which takes into account the demand for health insurance itself.

billion (81 percent of sales). Thus, these calibrations suggest that product liability exemption has the potential to increase welfare quite substantially, and naturally more so if liability costs account for a large percentage of a drug's costs. Moreover, the figure also reveals that the welfare gains from a product liability exemption are primarily driven by gains in consumer welfare, not gains in producer profits.

These results suggest the possibility of substantial increases in consumer welfare when firms are exempted from product liability lawsuits for those activities that are well regulated by the FDA. However, several points need to be addressed in evaluating this argument. First, the level of FDA regulation may interact with the existence of product liability. For example, perhaps the threat of liability prods the FDA to take a stronger stance on safety. Or perhaps if product liability did not exist, perhaps the FDA would increase safety further because it would then take full blame for product failures. Second, drug safety is probably a function of several activities, such as pre-clinical testing, clinical testing, proper manufacturing, proper warnings, and post-market surveillance. Clearly, product liability may have a role for safety outside of the activities regulated directly by the FDA. In particular, regulations on the behavior of firms after the drug or medical product has reached the market are much harder to monitor and enforce and product liability may play a more productive role here. Third, the costs of duplication may have some corresponding benefits, making analysis of their relative size important. In general, more evidence is needed on the share of overall costs that go towards legal costs, but in the vivid case of the diphtheria-pertussis-tetanus (DPT) vaccine, Manning (1994) estimated that liability initially accounted for 15 percent of the vaccine's price and rose to 90 percent of the vaccine's price as legal liabilities increased. However, with these concerns duly noted, it remains true that when

duplication exists between regulation and product liability, consumers in particular will suffer welfare losses from the corresponding price increases.

Dynamic Efficiency and The Tradeoff between Safety and Time to Market

As the value of new medical technologies may be very high, delays in their introduction is often particularly costly. Therefore, looking at the degree of investment in product safety in a static sense does not take into account the reductions in dynamic welfare that occur by lengthening the time it takes for products to reach consumers. In Philipson et al (2005), we discuss the exact welfare implications of this issue and provide a methodology of how to estimate the efficiency effects of the speed versus safety tradeoff that is perhaps the central tradeoff of the FDA. In general, the dynamically optimal safety is lower than the statically optimal level due to the extra costs of delayed marketing of valuable technologies.

As discussed earlier, the Prescription Drug User Fee Act of 1992, along with its extensions in 1998 and 2003, were a series of acts that levied user fees on drug manufacturers, in exchange for faster review times. The effects of this act can be used to illustrate the speed-safety calculations discussed in Philipson et al (2005). While this legislation has been praised for reducing drug approval times, it has also been criticized for reducing the safety of drugs on the market (see a discussion in Institute of Medicine, 2006). We argue that the gains in welfare from increased speed more than offset any losses in static efficiency from less safe drugs.³

The Effect on Speed

³ In evaluating the full impact of the Prescription Drug User Fee Act of 1992 one may consider the revenue aspects as well and whether user fees imposed on drug firms should be substituted for general taxes funded by the general population consuming drugs. Using general taxes may lower the excess burden of taxation if the user fees distort R&D investments. While this may be the case in principle, the distortions may be small given the small size of user- fees to any expected sales from the drugs involved.

Figure 3 plots survival curves showing the percentage of what are called New Molecular Entities awaiting approval over time, with curve for the time periods when the first period when the Prescription Drug User Fee Act of 1992 was in effect and the period after it was first reauthorized, along with two earlier periods. Each curve shows the percentage of drugs submitted for approval that has not yet been acted upon within a given number of months after submission of the New Drug Application. Survival curves from more recent time periods are clearly separate from and lower than are those from earlier periods. The more rapid decline in survival curves after the passage of the Prescription Drug User Fee Act of 1992 indicates gains in speed. 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 Prescription Drug User Fee Act of 1992, because the goals in the law involved review times rather than approval times.

We found that drug approval times fell by roughly 2 percent per year in the periods before 1992. After the passage of the Prescription Drug User Fee Act of 1992, approval times fell by 9-10 percent annually, and then about 5 percent annually after the legislation was first reauthorized from 1997-2002.⁴

The Effect of Speed on Consumer and Producer Surplus

Faster drug approval times will cause consumer and producer surplus gains to occur earlier. To get an idea of the effect of PDUFA on producer surplus, we returned to our data on life cycle sales and costs for a set of 663 drugs on the U.S. market between February 1998 and December 2002. Given our estimates of the effect of the Prescription Drug User Fee Act of 1992

⁴ We found that effects Prescription Drug User Fee Act of 1992 on approval times do not vary significantly across drug classes. Two exceptions are that during the period from 198 to 2003, after the legislation was reauthorized for the first time, the annual declines in approval time for anti-inflammatory drugs and anti-neoplastic (chemotherapy) agents are significantly larger than for other drugs, with annual declines for the former approaching 15 percent, and annual declines for the latter reaching about 10 percent.

on drug approval times, we valued greater speed by asking how much the present value of welfare would increase by allowing the observed stream of surplus to happen sooner. Using this method for valuing speed, and a 3 percent discount rate, the Prescription Drug User Fee Act of 1992 increased the present value of sales by roughly \$15 billion (1.31 percent of sales) while also increasing costs by \$3.89 billion (0.34 percent of sales). Overall then, the reform of 1992 increased producer surplus by roughly \$11 billion (0.96 percent of sales).

Calibrating the effects of the Prescription Drug User Fee Act of 1992 on consumer and social surplus was more complicated for two reasons. First, since consumer surplus must be inferred from quantity and price data alone, some assumptions on the nature of demand had to be made. Second, consumer surplus is lower before a patent expires and higher after it expires, since generic competition occurs, thereby reducing prices. Our major finding was that under a 3 percent discount rate, the 1992 legislation increased the present value of social surplus by between \$18-31 billion which amounts to about 1.6 to 2.7 percent of overall sales.

The Effect on Safety

These estimated increases in social surplus must be weighed against the potential losses due to the possibility of less safety in the drugs being released. We calculated how many life-years were lost as a result of additional unsafe drugs.

We used the Adverse Event Reporting System (AERS) to calculate the number of lives lost from drugs that were approved under the Prescription Drug User Fee Acts, but subsequently withdrawn. AERS is a database maintained by the Food and Drug Administration which includes patient, physician, and drug-company initiated reports of adverse drug reactions. Specifically, AERS provides reports on patient deaths, which we used to estimate the number of life-years lost. For each of the drugs that were approved under the Prescription Drug User Fee

Acts and subsequently withdrawn, we used AERS to calculate the number of fatalities attributed to these drugs during the entire time that they were on the market. Overall, our analysis found that about 55,600 life-years were lost from drugs that were approved under the years of PDUFA but were subsequently withdrawn. A reasonable range of estimates for the value of a life-year would be from \$100,000 to \$300,000. Thus, the losses due to reduced safety would range from \$5.6 billion to \$16.6 billion. Since the present value of social surplus was \$18 billion to \$31 billion, the gains from increased speed likely outweigh the costs.

Our estimate of costs is imperfect in a number of ways. For example, we look only at costs that involve loss of life, not the costs of causing illness. In other words, we only examined the effect of PDUFA on mortality, but not morbidity. This factor means that we tend to underestimate costs. On the other side, there are several reasons why our estimate would be biased toward overstating costs. First, we assume that all deaths reported in AERS were directly caused by the specific drug in question. Second, our approach assumed that all drugs that were approved under the Prescription Drug User Fee Acts and later withdrawn would not have been approved at all in the absence of the acts. Finally, our approach to estimating costs does not include the likelihood that the drugs withdrawn had health benefits to other consumers who were not adversely affected. Taking these factors together, it seems plausible to us that before the enactment of the Prescription Drug User Fee Act of 1992, safety was being overprovided at the expense of getting new medical products to consumers in a timely manner.

Concluding Remarks

Relatively little explicit research has been done by economists on the efficiency tradeoffs involved in the main policies of the Food and Drug Administration. Our discussion has brought

forward two main policy issues. First, the static issue, which suggests that, given the existence of regulatory oversight through the FDA, there may be a case for a product liability exemption for manufacturers of new drugs and medical products – at least as related to tasks already well-regulated by the FDA. Second, the dynamic issue of assessing the central speed safety tradeoff of the agency implies that the dynamically optimal level of safety is lower than the statically optimal one. The analysis we discussed suggests that speed of new product approval was underprovided before the Prescription Drug User Fee Act of 1992, although more analysis would be needed to see whether additional gains in speed at the expense of drug safety might be worthwhile. It is important to note that the analysis of both of these issues may extend more broadly to other markets as well.

Our analysis also suggests several directions for future research. First, with regard to the static efficiency question of assuring the appropriate level of product safety through a combination of regulation and product liability, one important question is how product liability might be made more efficient. Damages in such cases are typically awarded by juries, who are not spending their own money. If juries are likely to award inefficiently high damages, then pharmaceutical firms will produce products that are inefficiently too safe, or may exit the market entirely as has been observed in the case of vaccine development (Manning, 1994). Another important question in this area is to examine the incidence of liability costs under product liability. Ultimately, the economic incidence of product liability falls on consumers, in the form of higher prices. In effect, product liability acts as mandatory product insurance for consumers. However, this type of mandatory insurance may involve cross-subsidization or unfair pricing of risk. We believe more work needs to be done understanding the efficiency effects of this type of mandatory insurance, or “medical warranties”.

Second, with regard to the dynamic efficiency analysis, there are many policies whose efficiency ultimately comes down to the evaluation of the discussed speed-safety tradeoff and should be analyzed as such. For example, when the FDA requires certain labels and marketing regulations, this affects the speed safety tradeoff. Another example is the use of biomarkers, which are physical traits used to monitor the progress of a disease, e.g., the presence of a particular hormone, to replace traditional outcomes, such as mortality. The tradeoff introduced by use of bio-markers is again the speed safety tradeoff; using the marker as an outcome in the clinical trial could reduce the length of time needed to conduct the trial, however, a shorter trial would also provide less information about safety.

Third, another important general issue to analyze concerns off-label use of drugs --that is, use for indications that the drug has not been approved for by the FDA. Such use is legal, but little systematic evidence exists whether more unsafe use is entailed by such unregulated uses or about the speed with which such use diffuses to potential patients.

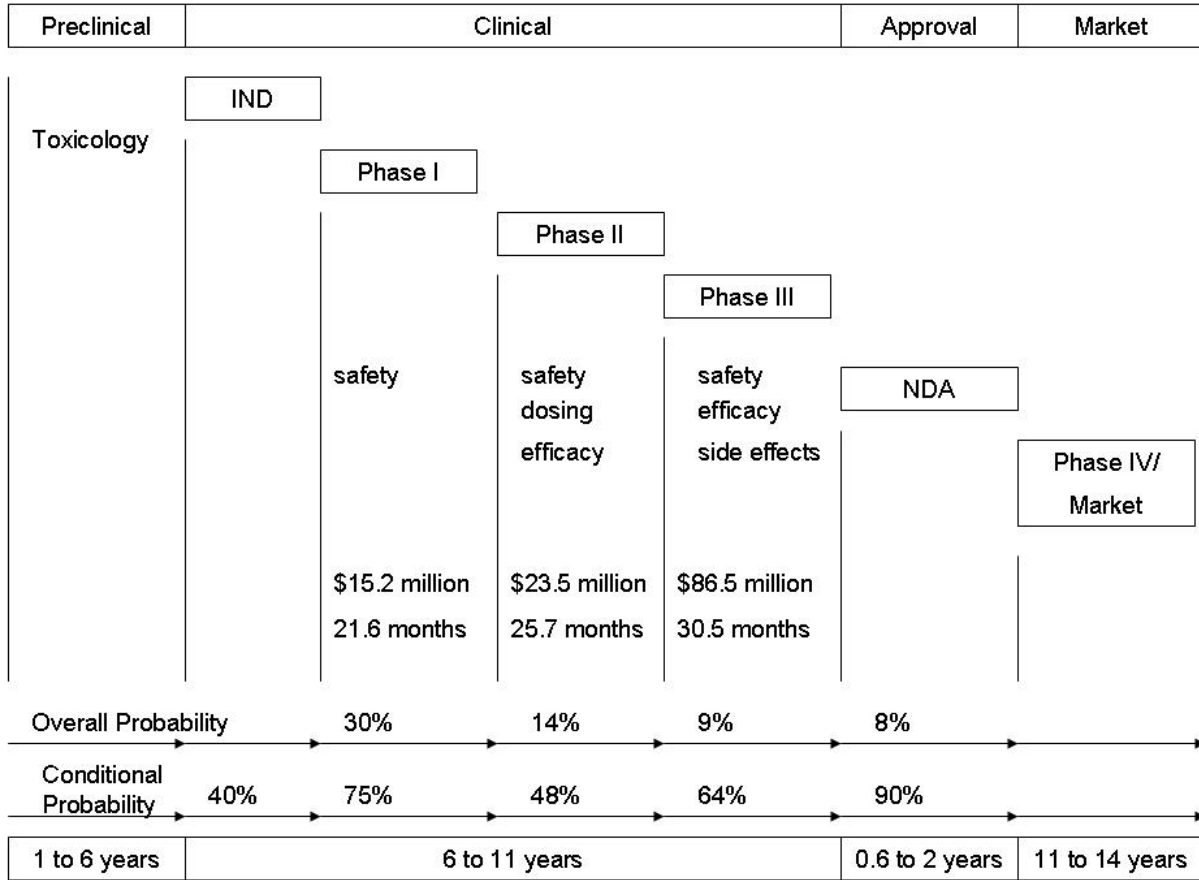
Fourth, more analysis is needed on the impact of FDA and the value of procedural innovations. What often happens now is that new devices or drugs, which are patentable, require for their use a new medical procedure, which is not in itself patentable. The FDA approves the new devices or drugs, but only comments on the procedures in passing. For example, stents are devices that are surgically implanted in a blood vessel in order to keep it open. While the FDA has authority over the stents themselves, it has little authority over the surgical procedures used to place the stents. An interesting question is how the FDA affects the incentive to innovate in procedures.

More generally, although often commented on, explicit analysis of the efficiency effects of the policies of the Food and Drug Administration is not as well developed as for many other

regulatory agencies. However, it bears great promise. In an agency dominated by the thinking of doctors and lawyers, economic analysis can offer useful methods by which to produce more explicit- and evidence-based evaluation of its policies, mimicking better the high standards set for the products it oversees.

Figure 1

An Overview of the Drug Development Process

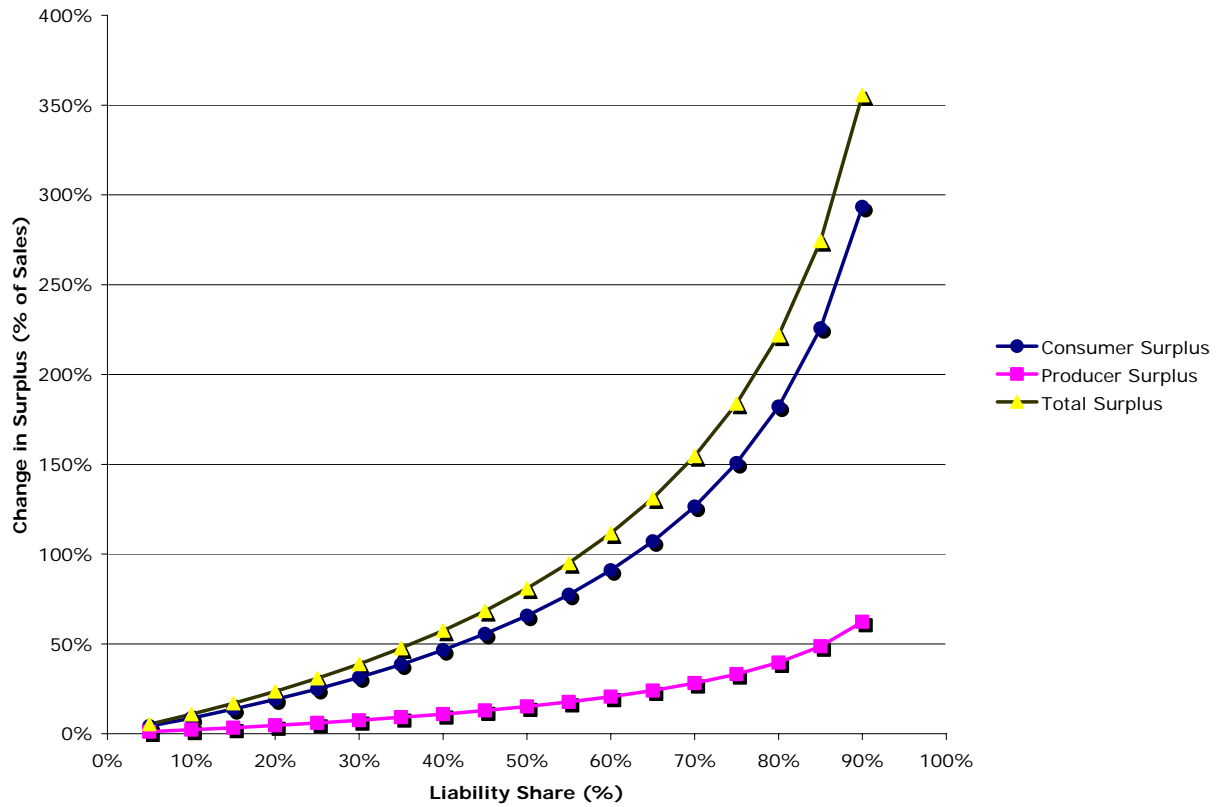


Sources : Dimasi et al (2003).

Notes : The line marked “overall probability” is the unconditional probability of reaching a given stage. For example, 30% of drugs make it to phase I testing. The line marked “conditional probability” shows the probability of advancing to the next stage of the process, conditional reaching a given stage. For example, the probability of advancing to phase III testing conditional on starting phase II testing, is 48%.

Figure 2

Effects of a change in liability regime on welfare

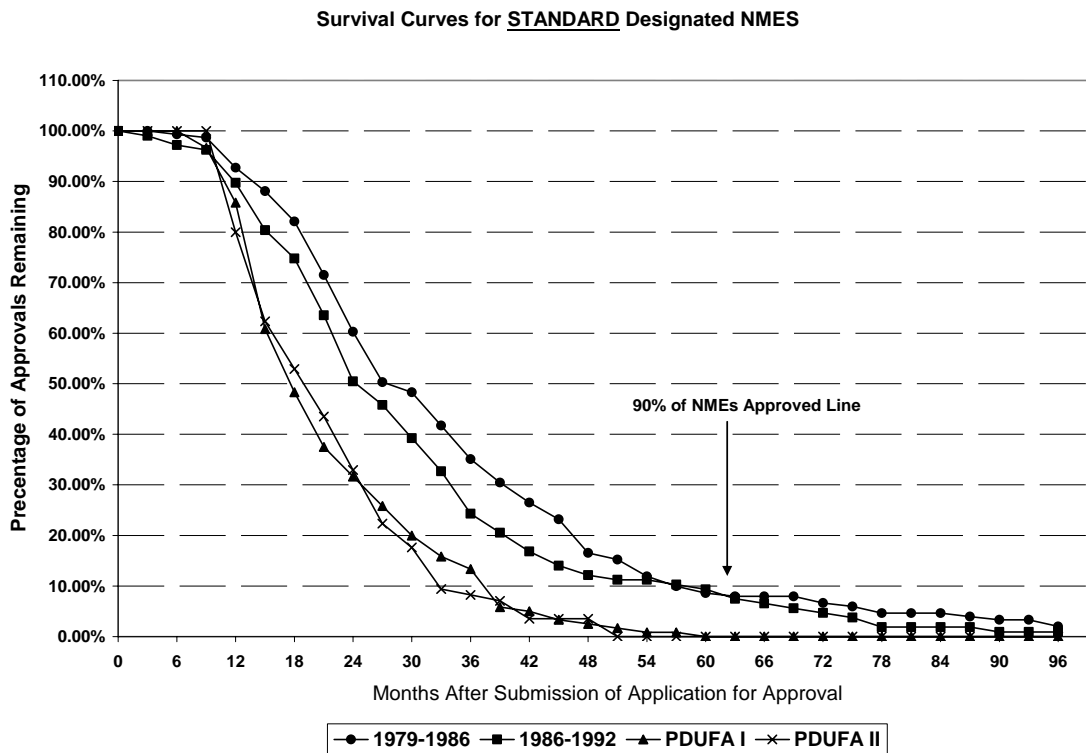


Sources : Philipson and Sun (2007)

Notes : The increases in surplus as reported as a percentage of sales. Total sales for the sample of drugs we consider is \$1,149 billion.

Figure 3

Share of undecided applications as function of time pre- and post PDUFA



Source : Philipson, Berndt, Gottschalk, and Strobeck (2005).

Acknowledgements

We are thankful to all editors of JEP for comments that greatly improved the paper, as well as Steven Garber at RAND and seminar participants at The University of Chicago, RAND and the 2007 IHEA Meetings in Copenhagen for comments. Philipson served as Senior Economic Advisor to the Commissioner of the FDA from 2003-2004, but all views expressed in this paper represent the views of the authors and do not necessarily reflect the views of the FDA. We are grateful to the Bing Center for Health Economics and the Institute for Civil Justice at the RAND Corporation, as well as the Chicago Center for Excellence in Health Promotion Economics and the George C. Stigler Center for Study of Economy and the State at the University of Chicago, for financial support.

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