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Dying for FDA Reform

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This year, Congress is considering a variety of legislative changes that would substantially affect the regulation of pharmaceutical drugs. There is growing momentum for congressional action to address several perceived drug safety problems, but all of the proposals under consideration would harm, not improve, patient safety by making it more difficult to get promising new drugs approved and into the hands of doctors and patients. These ill-conceived policies would also increase the already astronomical costs of bringing these medicines to market, raise prices, and reduce incentives for developers to undertake experimental projects.

The FDA and Political Influence. As recently as 10 years ago concerns about pharmaceutical regulation focused primarily on "drug lag"—slow reviews and approvals by the Food and Drug Administration (FDA) that put Americans at a disadvantage relative to consumers in other countries. But, in recent years, the concern has shifted to what might be called "drug leap"—allegations of hurried approvals with insufficient attention paid to drug safety, resulting from too-close a relationship between regulators and industry. Several highly publicized events have heightened public concern about drug safety, including possible adverse cardiovascular effects associated with non-steroidal anti-inflammatory drugs (NSAIDs), allegedly inadequate warning labels on antidepressants, and rare but life-threatening infections after treatment with the multiple sclerosis drug Tysabri.

Contrary to these perceptions, however, FDA has actually become progressively more cautious and slower to approve new medicines during the past decade. Although legislative changes—such as the Prescription Drug User Fee Act of 1992 and the FDA

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Modernization Act of 1997—and various internal changes within the agency have been intended to modernize and streamline the drug development process, the rate at which new drugs appear in the marketplace has slowed considerably.

FDA's Center for Drug Evaluation and Research (CDER) approved a mere 22 new medicines with truly novel chemical compounds in 2006, and only 20 in 2005.[1] That is down from a recent high of 53 in 1996 and 39 in 1997. Yet, from 1993 to 2004, the number of CDER personnel rose by 50 percent, from about 1,400 to over 2,100, and total funding allocated for drug reviews more than tripled, from approximately $130 million to over $430 million.[2]

Although the length of time it takes FDA to review and approve New Drug Applications (NDAs) has fallen since the early 1990s, essentially all of that decline occurred between 1993 and 1998.[3] Nevertheless, at an average length of nearly one year, those reviews still substantially exceed the 180-day action period mandated by the Food, Drug and Cosmetics Act.[4] Furthermore, that time period measures only the agency review of a submitted application, which comes after as long as 10 years—and sometimes longer—of actual testing.

The regulatory burdens on the clinical testing phase of development have also increased substantially since the 1980s. Since then, the average number of clinical trials conducted to support each NDA has more than doubled, and the average number of patients in those trials has nearly tripled.[5] Such additional burdens do little to make new medicines safer, but they delay or block the availability of new treatments, and make those new drugs that do appear on the market vastly more expensive.

The Benefit of New Drugs. There is considerable evidence that drugs often improve the span and quality of life in a remarkably cost-effective way. And newer drugs typically confer important therapeutic advantages over older ones. According to a recent National Bureau of Economic Research study, patients suffering from serious illnesses such as heart disease, diabetes, and cancer, who were prescribed relatively newer drugs were more likely to live longer than those taking older drugs.[6] For drugs approved before 1970, the estimated mortality rate was 4.4 percent, whereas the mortality rates for drugs approved during the 1970s, 1980s, and 1990s were 3.6 percent, 3.0 percent, and 2.5 percent respectively.

Notwithstanding such findings, many FDA critics insist that the agency has, in recent years, negligently approved dangerous drugs and then failed to monitor them sufficiently. In the wake of several high-profile drug safety scares, bashing FDA has become *de rigueur* for many in Congress and the media. Members of both major political parties regularly accuse the agency of recklessly speeding drugs to market for the sake of corporate profits at the expense of patients' health.

Perhaps paradoxically, however, longer reviews *do not* improve drug safety. Research conducted by FDA itself shows that the rate of drug approval withdrawals has remained essentially unchanged over the last 25 years, despite rising and falling approval times

during that period.[7] On the other hand, the health benefits of faster approval decisions far outweigh the risks associated with the small number of unsafe drugs that occasionally do make it to market. A study by economists from the University of Chicago, Massachusetts Institute of Technology, Biogen Idec Inc., and Westfield Capital looked at all 662 drugs approved by FDA from 1979 to 2002 and concluded that, even if every withdrawn drug provided no benefits at all, the faster pace of approvals beginning in the 1990s benefited patients with an extra 180,000 to 310,000 years of life—three to five times greater than the worst case estimate of harms.[8]

Furthermore, many of those drugs that are later withdrawn often prove beneficial to the vast majority of patients who use them. The diabetes drug Rezulin, for example, is believed to have caused the tragic loss of 63 lives due to liver complications before it was pulled from the market in 2000.[9] But more than 500 Americans die every day from complications of diabetes itself.[10] After balancing the risks, even with the knowledge that Rezulin raised the risk of liver toxicity, FDA initially approved the drug because its benefits to diabetics were so substantial. The agency decided it was better to warn doctors and patients of the risks, and allow them to make their own risk-benefit judgments in individual cases. Often overlooked is the fact that FDA only asked the manufacturer to withdraw Rezulin after two new drugs in the same chemical class were shown to provide similar benefits with less risk.[11]

While it was on the market, Rezulin offered substantial benefits to millions of diabetics. When FDA considered withdrawing the drug, many doctors and patients pleaded with the agency to keep it available to them. University of California, San Diego School of Medicine Professor Steven Edelman told the agency that the benefit to most diabetics using Rezulin was so great that, "You can't buy this drug back from these patients."[12] Yet, even today, some FDA critics view the Rezulin approval as a failure, as they do the small number of other supposed "approval mistakes."

Indeed, recent criticism from Congress, the media, activists, and the public regarding drug safety has caused an already risk-averse agency to become even more conservative and defensive in its decision making. In September 2006, the biotechnology firm Genentech announced that approval of its colon cancer drug Avastin for a new indication, the treatment of breast cancer, would be delayed by at least a year because FDA medical reviewers requested additional data and reanalysis of previously submitted data in a way that differed from an earlier agreement with the regulators.[13]

Another recent example involves FDA requirements for testing an already approved drug, doxepin, for a new indication. That drug was approved for the treatment of depression in 1969, but Somaxon Pharmaceuticals is now testing it in very low doses for use as a sleeping aid. FDA officials initially assured the company that it could begin human clinical trials without first doing animal tests because of doxepin's long history of safe use and because Somaxon was using only about 1 to 8 percent of the dose used to treat depression.[14] However, in May 2006, after Somaxon had completed several clinical trials, regulators unexpectedly asked the company for a full battery of animal testing. Animal testing is usually considered to be "pre-clinical," so it is difficult to understand

the logic of requiring animal testing for an almost 40-year-old drug that is undergoing trials for a new indication, at a far lower dose than is normally used.

Post-Approval Monitoring. In the wake of the recent withdrawals, some critics also accuse FDA of being too lax in monitoring the safety of drugs already on the market and negligent in informing the public of emerging safety problems. In response, the agency adopted several initiatives designed to increase adverse event surveillance. One of these was the creation of a Drug Safety Board to oversee and advise FDA's approval arm on patient safety issues and to manage the flow of emerging safety information to patients and health care professionals.[15] Another is the Drug Watch Program, which will make such "emerging safety information" publicly available. According to FDA, the latter program "is not intended to be a list of drugs that are particularly risky or dangerous for use." Rather, its purpose is "to share emerging safety information before [FDA personnel] have fully determined its significance."[16]

It is difficult to predict what physicians and other health care providers—let alone members of the public—will do with such preliminary and inconclusive data, however. There is a difference between indiscriminate data and useful information, and the Drug Watch Program seems destined to provide far more of the former. Indeed, as then-FDA Deputy Commissioner Scott Gottlieb noted, "Information that could influence clinical medical practice needs to be made available more quickly, and more widely, *after it has gone through a deliberative scientific process that firms up its meaning and the magnitude and the veracity of its conclusions*."[17] Yet Gottlieb described the data that would appear on Drug Watch as being "still un-scrubbed by scientific rigor."

Moreover, given FDA's current desire to demonstrate a commitment to drug safety, and the difficulty of proving a negative, one wonders how a "suspect" drug would ever be able to clear its name and get off the Drug Watch list. It would be far more constructive to update product labeling quickly and continuously once regulators get past the stage of merely "attempting to assess the meaning and potential consequences of emerging safety information," and have actually "determined the significance" of such information. It bears repeating that individual data points rarely provide useful information. Individual adverse events are not necessarily signs that a drug has safety problems—let alone problems severe enough to require a change in prescribing practices or withdrawal from the market.

Ironically, premature and indiscriminate reporting of adverse event information can itself cause harm to patients. Deciding exactly when a string of isolated cases becomes a pattern indicative of a bigger problem—a safety "signal"—is often a challenge. When a patient dies or his condition deteriorates, it is rarely clear whether the medicine or the pre-existing condition is to blame. Nor is it likely to be clear, even after several adverse events, whether the drug's overall benefits no longer outweigh its risks. But "erring on the side of caution," and reporting every suspected adverse event as though it conveyed useful information, can lead some patients to cease taking a medication that does them far more good than harm. Thus, issuing an early warning about a drug that turns out not to

be especially dangerous (a "false positive") harms people just as surely as mistakenly leaving a faulty product too long on the market (a "false negative").

FDA Control of the Practice of Medicine. A further sign of greater risk aversion is FDA's increasingly aggressive use of post-marketing "risk minimization action plans" (RiskMAPs). These can include the submission of additional safety information, including larger safety studies to screen earlier for relatively rare potential adverse reactions, greater restrictions on distribution and advertising, and so on. In March 2005, for example, the RiskMAP that accompanied FDA's approval of the diabetes drug Symlin prohibited the manufacturer from conducting any direct-to-consumer advertising or even medical journal advertising for one year following approval, and it restricted promotion primarily to physicians who specialize in diabetes management and who are supported by certified diabetes educators.[18]

This kind of ban on advertising is outside FDA's statutory authority and may well be unconstitutional.[19] Perhaps more important, banning pharmaceutical ads conflicts with the conclusions of countless physicians and of the Federal Trade Commission that direct-to-consumer advertising benefits consumers by leading them to consult their doctors about treatments for potentially serious conditions and by spurring the competition that puts downward pressure on drug prices.[20] Indeed, in its own guidance to industry, FDA cited "promotional techniques such as direct-to-consumer advertising highlighting appropriate patient use or product risks" as an example of how to use a RiskMAP.[21]

This sort of inconsistency from FDA is greatly problematic for companies that have invested substantial sums in research and development, but it is not uncommon. Consider FDA's recent actions on the post-approval risk management of two drugs, Tysabri and Rituxan. In late 2004, Tysabri was approved for the treatment of multiple sclerosis, a debilitating autoimmune disease that affects the central nervous system. But, because Tysabri works by suppressing certain components of the immune response, regulators, clinicians, and the product's developers were sensitive from the beginning to the possibility of infections as a side effect.

In early 2005, with several thousand patients already being treated with Tysabri, it was discovered that three had contracted progressive multifocal leukoencephalopathy (PML), a rare and often fatal neurological disorder caused by a virus. The manufacturers voluntarily withdrew Tysabri from the market, but, after the analysis of new safety data, an FDA advisory committee recommended it be put back on the market with revised labeling. FDA went far beyond adding more prominent warnings, however, and insisted on a complex RiskMAP that imposes onerous restrictions on the use of Tysabri. They include limited distribution and additional education and monitoring requirements for patients, prescribers, pharmacies, and infusion centers.[22]

The drug Rituxan is a treatment for rheumatoid arthritis and certain kinds of lymphomas. Like Tysabri, it acts by suppressing elements of the immune system and has also been linked to PML. There have been 23 confirmed cases of PML in patients receiving Rituxan for the approved indication of non-Hodgkin's lymphoma and two cases in

patients being treated experimentally for systemic lupus erythematosus.[23] But, unlike Tysabri, Rituxan has never been subject to a RiskMAP. And, in spite of the new cases of PML in patients with lupus—as well as the fact that Rituxan also is being considered for treating multiple sclerosis—FDA was content merely to update Rituxan's package insert. Leaving aside the question of whether Rituxan should be subject to greater restrictions or whether Tysabri deserves fewer, the point is that FDA's inconsistency sends mixed signals and creates uncertainty, the bane of patients, doctors, and drug companies alike. Yet legislation now being considered in the Senate would force FDA to expand its use of Risk MAPs, which the bill calls Risk Evaluation and Mitigation Strategies (REMS).[24]

Conclusions. Defenders of the present, risk-averse system argue that lower efficiency is the price of safety. But this is a false tradeoff. Congress could better promote high standards of safety and greater efficiency by recognizing that getting new drugs to market helps to save lives and by fundamentally reforming the way in which drugs are regulated. Ending regulatory excesses—especially politically driven ones—and introducing competition into regulatory oversight would allow more patients to benefit from the greater number of medicines made available to them in a timelier way.

Efforts during the 1990s to increase the pace of new drug approvals, such as the 1992 Prescription Drug User Fee Act, were useful, but only partial improvements. As discussed above, the speed of approval only measures the relatively brief time span between the submission of a new drug application for review and FDA's approval. Most of the pre-approval time that a drug spends under FDA jurisdiction consists of the far longer interval between the initiation of clinical testing and the submission of the application. And this investigational stage has become longer and more burdensome during the past two decades, more than offsetting the modest gains in speedier approvals.

Although meaningful change in the drug approval process will require legislative action, recent congressional interest in drug regulation has taken the form of politically motivated investigations of alleged under-regulation or insufficient attention to product safety. Ironically, it is Congress's failure to carry out its oversight and legislative role responsibly that has permitted FDA's risk-averse culture to become progressively worse and more entrenched. All of the newly introduced checks on FDA's drug approvals—such as the Drug Safety Board and the Drug Watch Program, and more recent proposals along these lines—are asymmetrical, in the sense that they primarily address narrowly defined concerns about safety, but do not address the lost benefits of drugs that are needlessly delayed or abandoned.

No genuine reform is possible until Congress acknowledges that no medicines are risk-free and even drugs that pose considerable risk may, on balance, provide net therapeutic benefits. Congress must then begin to force an evolution in FDA's culture of risk aversion, which unnecessarily delays product approvals. FDA's senior and mid-level managers should be made more accountable—especially for scientifically dubious policies and needless delays in getting new drugs, vaccines and medical devices to the patients who need them. The American public is literally dying for reform.

Notes

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