

An Innovative Drug Industry? Well, No; [FINAL Edition]

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CAMBRIDGE, Mass.

My friend Jim Cordy was 40 when he was diagnosed with Parkinson's disease. That was 16 years ago. There is no medicine to slow the inexorable neurodegeneration that is the underlying cause of Jim's condition, only drugs that provide short-term symptomatic relief. Since I met Jim four years ago, the effectiveness of this medication has faded, and he has become increasingly debilitated; in 10 years, he may be virtually paralyzed. But Jim is hopeful: Surely a breakthrough drug is just around the corner. Hasn't the federal government doubled its spending on biomedical research in the past five years? And what about the scientific revolution spawned by the sequencing of the human genome?

Jim's hopefulness is understandable. I guarantee he'll see tremendous advances in our scientific understanding of Parkinson's in the near future. But when it comes to new medicines, I fear he may have to settle for new versions of existing drugs for more prevalent conditions such as allergies and heartburn.

The popular image of America's productive and innovative pharmaceutical industry is a historical myth. The truth is that the system that currently regulates the development and approval of new drugs discourages innovation. Unless it's significantly reformed, there are likely to be few breakthrough medicines for Jim or millions like him who suffer from life-threatening or debilitating diseases.

Unfortunately, rational discussion of this dire situation has been overshadowed by the simplistic debate over prescription drug prices. Despite their pronouncements to the contrary, neither the politicians nor the pharmaceutical companies are acting in the public's best interest.

The politicians who support reimporting drugs from Canada are sacrificing future medical advances to save money and win votes in the short term. It's disingenuous to claim that reimportation is consistent with a free-market economy, since Canada's lower prices result from government-mandated price controls. Such controls, while lowering the price of existing drugs, would make it impossible for the pharmaceutical industry to engage in the type of innovative research necessary to produce breakthrough medicines.

Rather than advance this reasonable argument and call for reform, the pharmaceutical industry, for its part, has raised dubious claims about the safety of Canadian drugs. This transparently self-serving campaign has added to the feeling that the industry is not entirely trustworthy. It is difficult to sympathize with an industry that has the highest profit margin in the country, especially when, to protect those profits, it has increasingly turned away from its history of innovation to focus on producing and aggressively marketing modified versions of existing drugs for big-market conditions, known in the industry as "me-too" drugs.

The trend away from innovative drugs started years ago. The FDA classified 53 percent of the drugs approved between 1982 and 1991 as offering "little or no therapeutic gain." Between 1996 and 2001, things got worse: The pharmaceutical companies' spending on research and development increased by 40 percent, but the number of new drugs reaching the market decreased by 50 percent. Of 31 "blockbuster" drugs (those with annual sales of \$1 billion or more) launched between 1992 and 2001, 23 were me-too drugs for common conditions such as allergies and inflammation. Now, get ready for an influx of Viagra mimics. But do we really need five indistinguishable versions of Viagra, when they divert resources that could be used to develop innovative drugs for life-threatening diseases?

The Orphan Drug Act of 1983 was intended to promote the development of drugs for diseases that affect fewer than 200,000 Americans by offering incentives such as market exclusivity and tax credits. Unfortunately, this legislation has been only moderately successful, as its incentives are dwarfed by the profitability of me-too drugs. This is because the legal system that regulates our pharmaceutical industry forces manufacturers to choose between maximizing profits and improving public health. This system, rather than the surface issue of drug prices, should be the real focus of legislative concern.

Take the patent law. A drug patent gives a company the exclusive right to sell that drug for 20 years; after that, generic competitors may enter the market and provide the same drug at lower prices. This system was created to reward the innovator, but today, it rewards the imitator. That's because the requirements for patenting a particular drug have not significantly changed for 50 years. The science of drug discovery, though, has changed dramatically, from a trial-and-error process to one targeting a particular mechanism of action. Drugs that mimic the mechanism of action of Viagra, Vioxx or Lipitor may be patented even though

they are not innovative, do not serve an unmet medical need, and are often no more effective than the "trailblazers" on which they are based.

To make matters worse, the me-too drugs, when aggressively marketed, typically become bigger sellers than the trailblazers. Me-too drugs are much more likely to win approval than novel drugs and are more easily developed than trailblazers. Eliminating undeserved patent protection for them would encourage development of breakthrough medicines.

Then there's the expensive, time-consuming approval process. To win approval from the FDA, a drug must be demonstrated as safe and effective against a particular condition through three stages of clinical trials. In Phase 1, safety is evaluated for six months in a group of up to 100 healthy volunteers. In Phase 2, safety and efficacy are evaluated in a group of approximately 200 patients, who suffer from the condition in question, for approximately two years. Finally, Phase 3 trials test safety and efficacy in thousands of patients for up to four years. Phase 3 trials account for roughly 50 percent of the total cost of bringing a drug to market. Replacing the Phase 3 requirement with a conditional approval, based on successful completion of Phase 1 and Phase 2, would reduce the price of new drugs while making them available to patients more rapidly.

There are also scientific reasons to replace Phase 3. The reasoning behind the Phase 3 requirement -- that the average efficacy of a drug is relevant to an individual patient -- flies in the face of what we now know about drug responsiveness. Very few drugs are effective in all individuals. In fact, most are not effective in large portions of the population, for reasons that we are just beginning to understand.

It's much easier to get approval for drugs that are marginally effective in, say, half the population than drugs that are very effective in a small fraction of patients. This statistical barrier discourages the pharmaceutical industry from even beginning to attack diseases, such as Parkinson's, that are likely to have several subtypes, each of which may respond to a different drug. These drugs are the underappreciated casualties of the Phase 3 requirement; they will never be developed because the risk of failure at Phase 3 is simply too great.

The irony of the Phase 3 requirement is that physicians can prescribe a drug even if it hasn't been shown to be clinically effective. Once the FDA has approved a drug based on its effectiveness against one condition, it can be prescribed for any other condition. This practice recognizes that your physician is best equipped to evaluate all the available information and advise whether you could benefit from a particular drug. About 40 to 50 percent of all drug use is for such unapproved, or "off-label," uses. Some drugs that "failed" in Phase 3 trials for one condition, but were approved for another, are still widely prescribed for the first because physicians agree that the evidence shows they can be effective.

Then there are drugs like Neurontin, an off-label blockbuster, with more than 80 percent of its sales being for unapproved uses. Though approved by the FDA for refractory epilepsy and pain related to shingles, Neurontin is more widely used for bipolar disorder, social phobia, panic and neuropathic pain. Even though its effectiveness against these prevalent conditions has not been tested in FDA-approved Phase 3 trials, encouraging data from small academic clinical trials and anecdotal reports of its effectiveness have convinced physicians that Neurontin can work.

If expensive Phase 3 trials were eliminated, patients using conditionally approved drugs could be closely monitored by their physicians and the FDA. This kind of public trial system would guarantee that patients would be rapidly informed of all clinical findings. After two to three years of carefully documented clinical use, full approval could be granted. This way, all patients, many of whom would not meet the strict requirements for inclusion in a Phase 3 trial, would have access to new drugs, and drug companies could take more risks on innovative ideas, since development costs would be cut in half.

As Jim Cordy's Parkinson's disease progresses, he will have the right to weigh for himself the risks and benefits of several experimental brain surgeries that could improve his symptoms. These procedures do not work for everyone, and they do involve risk. Drugs are no different. Surgeons are rightly encouraged to develop new breakthrough procedures. So why do we support a system that discourages pharmaceutical companies from even attempting to find a cure for Jim and others like him?

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