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CLINICAL RESEARCH SPONSORED BY PHARMACEUTICAL COMPANIES

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Americans spend about twice as much for brand-name prescription drugs as Europeans and Canadians. Furthermore, spending for prescription drugs is increasing in the U. S. at an unsustainable rate. There are three reasons: greater overall use of drugs (i.e., volume); higher prices for new drugs; and rapid price escalation of drugs already on the market, particularly top-selling ones. In fact, average prices for the top-selling drugs increased last year at more than twice the inflation rate.

The industry, while acknowledging the high prices, portrays this as something of a success story. We get our money's worth, the drug companies say, in the form of a steady stream of miracle drugs that improve and extend lives, and may even save money in the long run, because they avert more expensive forms of medical care, like hospitalization. Furthermore, skyrocketing prices, the companies say, are necessary to cover their research and development (R&D) costs – a claim that implies that they spend most of their money on R&D, and that after they pay for it, they have only modest profits left over. Doing anything to regulate prices, as in Europe and Canada, they say, would choke off R&D and stifle innovation.

What I want to do here is examine this argument. First, I'll address three questions: (1) How much do drug companies spend on R&D? (2) How much do they have left as profits? and (3) How innovative are they anyway? I'll conclude by looking at the quality of industry R&D, and how it could be better regulated. I want to make it clear that my comments will be focused particularly on the situation in the U. S., not only because this is what I know best, but also because the U. S. is the major profit center for all the large multinational drug companies and therefore of most interest to them, too.

Contrary to the industry's public relations, big drug companies spend relatively little on R&D -- far less than they spend on what most of them call marketing and administration and less even than they have left over in profits. Let's look at a few figures for 2002. That year the top ten American drug companies had sales of $217 billion. By their own figures, they spent 14 percent of that on R&D. But they spent over twice as much, a staggering 31 percent of sales (or about $67 billion), on marketing and administration. And they had 17 percent left over as profits – after all their expenditures. That's quite a profit margin. For comparison, the median profit margin for the 500 biggest companies in the U. S. was only 3.1 percent of sales that year. In fact, for well over two decades,

drug company profit margins have been three to six times as high as the median for all the Fortune 500 companies. With this record, there is simply no way this industry can be considered risky, despite rhetoric to the contrary. There is nothing high-risk about companies with such profits.
The recent claim that drug companies spend on average $802 million to bring each new drug to market is based on secret, proprietary data and wildly inflated, but whatever they spend on R&D, if they spend more on marketing and have more left over as profits, they can hardly claim that high prices are necessary to cover their R&D. Instead, high prices are necessary to cover their huge marketing expenditures and maintain their enormous profits.

The important issue is not how much drug companies spend on R&D, but whether we get our money's worth. In the rest of my talk, I'll make the case that we don't. Remarkable as it seems, only a small fraction of drugs now coming to market are innovative in any meaningful sense of the word. In the six years 1998 through 2003, of the 487 drugs that entered the market, fully 78 percent were classified by the FDA as likely to be no better than existing drugs. And 68 percent weren't even new drugs at all, but just old drugs in new forms or combinations. In other words, the major output of the industry is not important new drugs, but minor variations of drugs already on the market – called "me-too" drugs. For example, the top-selling drug in the world, Pfizer's Lipitor, is a me-too drug -- the fourth of six cholesterol-lowering drugs of the same type. There are now whole families of me-too drugs, and little reason to think one is better than another at comparable doses.

The few truly innovative drugs usually stem from publicly-funded research done at government or university labs. In the U. S., most of this work is sponsored by the NIH. Even within me-too families, the original is usually based on government-sponsored work. For example, the first of the Lipitor-type drugs, Mevacor, came on the market in 1987 and was based largely on university research. Sometimes the research is patented, but most often it's in the public domain – there for the taking.

Most of today's top-selling drugs have progenitors that date back to the 1980's or even earlier. Despite industry rhetoric, the drug companies are growing less and less innovative. They're just re-jiggering the same old drugs, just enough to get new patents, and relying on their marketing muscle to convince doctors and patients that they're producing medical miracles. In 2002, of the 78 drugs that entered the market, only seven were new chemical compounds classified as likely to be better than old drugs. And not one of the seven was made by a top ten American drug company. In fact, the big drug companies increasingly rely on licensing drugs from small biotech companies around the world. In other words, they're outsourcing their research. That may be legitimate, but it hardly supports their claim to be innovative -- and to be rewarded as though they were.

Most industry R&D spending goes for clinical trials – the end of the R&D process. While this is the least creative part of R&D, it is the most expensive. Companies that wish to sell drugs in the U. S. must demonstrate to the FDA that the drugs are safe and effective for their intended use, and this requires clinical trials. Drug companies also conduct many post-marketing studies to expand the use of drugs and buttress their marketing claims.

To get FDA approval, drug companies only have to compare the drug with a placebo, not with a drug already in use. That's why we usually have no idea whether a new drug is any better than an old one. It just has to be better than nothing – a very low standard indeed. It is this inexplicable loophole that makes it possible for drug companies to turn out one me-too drug after another, instead of undertaking the harder task of trying to discover innovative ones that target unmet needs.

Me-too drugs cash in on already established, highly profitable markets that are easily expanded. In fact, drug companies often promote diseases to fit drugs, instead of the reverse. They use direct-to-consumer ads to persuade essentially normal people that they have medical conditions that need ongoing treatment. Why? Because there are more normal people than sick ones, so the market is bigger and more easily expanded. Thus, millions of Americans come to believe they have dubious or exaggerated ailments like "generalized anxiety disorder," "erectile dysfunction," or "acid reflux disease." For every ailment or discontent there seems to be a drug – or many drugs.

Many me-too drugs target not diseases, but predisposing conditions, like high blood pressure or high cholesterol. I don't want to throw out the baby with the bathwater here. The appropriate pharmaceutical treatment of high blood pressure or high cholesterol is important and even life-saving for many people. But in recent years, the definitions of these conditions have been considerably broadened, so that in my view, many people are now taking drugs for these conditions when it's not at all clear they're of any net benefit or of more benefit than losing weight or exercising more.

We need to be concerned not only about the shift from innovation to imitation, but also about the reliability of the research on which the approval and use of drugs depend. I've been reluctant to believe that clinical research on prescription drugs is generally biased, but in the past couple of years I've had to conclude that it's biased far more often than I realized as an editor of the New England Journal of Medicine. I want to spell this out in some detail.

When a company seeks approval from the FDA, it's required to submit all of the clinical trials done for that purpose, but it needn't submit studies not done to support an FDA application. Furthermore, the FDA will not release all the trial results it has in its possession without the consent of the company. Nor does the company have to publish or otherwise publicize any of the results. That means many clinical trials never see the light of day. Companies, of course, are eager to publicize favorable trials, but

unfavorable results remain hidden – often within the FDA, which in this regard seems to put protection of industry "proprietary" interests ahead of the public health.

That's what Eliot Spitzer, New York's Attorney General, found in the case of research on GlaxoSmithKline's antidepressant, Paxil. Only the favorable results were published, but the FDA knew of studies showing Paxil was associated with an increased risk of suicidal thoughts in children. Let me give you another example. A few years ago, two researchers, Irving Kirsch and Thomas J. Moore, used the Freedom of Information Act to obtain FDA reviews of every placebo-controlled clinical trial submitted for initial approval of the six most widely used antidepressant drugs approved between 1987 and 1999 – Prozac, Paxil, Zoloft, Celexa, Serzone, and Effexor. What they found was startling. All six drugs were only minimally effective – on average the difference between drug and placebo was only 2 points on the 62-point Hamilton Depression Score – not enough to be clinically significant. And all were equally ineffective. Yet these drugs are widely considered by both doctors and the public to be highly effective, because only favorable results are publicized.

So we need to worry a lot about the suppression of unfavorable research. But we also need to ask whether we can rely on the favorable research that is published. I spent much of my professional life evaluating clinical trials for publication in the NEJM, and I can tell you that there are many ways to design a trial to make a drug look better than it really is – in addition to the obvious one of comparing it with placebo.

Since drug companies are for-profit businesses primarily responsible to their shareholders, they have a powerful incentive to make their drugs look good if they possibly can. Until a decade or so ago, that wasn't easy. Companies usually gave grants to independent university researchers who took full responsibility for carrying out the trials. Now, the companies have largely taken over that responsibility. They design the trials, analyze and interpret the data, and decide whether and in what form the results will be published. That gives them many opportunities to slant the research in favor of their drugs.

I'll give you just a few examples of how that can be done. Companies sometimes enroll only patients at low risk of side-effects, even though the drug is intended for use in more vulnerable populations. That way, it will seem to have fewer side-effects than it will in practice when it comes into widespread use. Or a new drug may be compared with an old one administered at too low a dose. That makes the new one look more effective, and it can be promoted as being stronger. Sometimes unfavorable data are simply omitted from a publication. Pfizer, for example, launched a one-year study to determine whether the painkiller Celebrex was easier on the stomach than older painkillers, but published only the first six months of the results, since the favorable effects disappeared in the second six months.

The fundamental problem is that drug companies have far too much control over research on their own products – how it's designed, how it's conducted, and how it's published. They usually hire private research firms to oversee the trials, which in turn hire private doctors to enter their patients in the trials. But they are all on the company payroll and if they want the business, they follow company instructions. Even when trials are conducted in academic centers, the researchers are often on the company payroll as consultants or advisers. These pervasive conflicts of interest raise concerns that much clinical research on prescription drugs is unreliable, and that in general, both doctors and patients have come to believe that drugs are more effective and safer than they are.

In the wake of the settlement of the Paxil case, there were calls to register clinical trials, whether favorable or not. That's a good idea, but it needs to be done right. Trials should be registered at inception in a central, publicly administered database. Initial registration would detail the design of the study – the kinds of patients to be enrolled, the drugs and doses, the outcomes to be measured, and how long the trial would last. That would prevent companies from changing the rules to suit the results, as Pfizer did when it published only the first six months of a one-year study and almost got away with it. At the end of the trial, the salient results would be added. Registration should include all trials, not just some of them, and be a requirement for enrolling human subjects. After all, using people for experimentation should entail public accountability. Clearly, the half-hearted industry promises of voluntary registries are not enough.

But as valuable as a proper registry would be, a more important reform would be to deal with the underlying conflicts of interest. In my book, I suggest ways to do this in the U. S., including the creation of a separate institute within the NIH to oversee clinical trials of prescription drugs before FDA approval. It makes no sense to rely on investor-owned businesses to evaluate their own products. And in the case of prescription drugs, it's way too dangerous.

Perhaps the single most important reform we could institute would be to require that drug companies compare their new drugs with old ones already on the market to treat the same condition. Drugs should generally not be approved by the FDA unless they're shown to be better in some way – more effective, fewer side-effects, or easier to take. Sometimes it may be deemed desirable to have more than one drug in a class on the market, but there's no excuse for having four or six or eight very similar drugs. The argument is often made that me-too drugs introduce price competition, but there's no evidence of that. Prices never drop in response to the introduction of a similar drug, and they're almost never promoted on the basis of price. They're promoted as though they were better, even though there's usually no scientific evidence to that effect.

This reform would pull the rug out from under the me-too market, and force the companies to do what they claim they're already doing – working on truly innovative drugs. It would also get rid of the need for those gigantic marketing expenditures. You can see from the direct-to-consumer ads that the drugs most heavily promoted are me-

too drugs. That's because the companies have to persuade both doctors and the public that there's something special about their particular me-too drug. If they had a truly important and unique drug, it wouldn't need to be advertised. Any company that comes up with a cure for cancer, for example, would not have to promote it.
The theme of this conference is "self-regulation." But self-regulation is what we have now – the status quo – and it is obviously failing. Indeed, how can we expect companies whose very survival depends on getting positive results in clinical trials to carry them out in a strictly impartial way? The notion of "self-regulation" is an oxymoron – a form of spin to try to ward off real regulation.

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