

Marcia Angell & Arnold S. Relman

Patents, profits & American medicine: conflicts of interest in the testing & marketing of new drugs

In the fall of 2001, the editors of thirteen of the world's medical journals made headlines when they jointly announced that they would not publish research reports about new prescription drugs unless the authors provided assurance that they had full access to the data and were responsible for the work.

This extraordinary step was a reaction to the growing control over clinical trials by corporate sponsors. Some of these sponsors do not permit investigators to see all of their own data, or to publish papers without prior approval.

The action of the editors – and the reason for their action – is merely one aspect of the story of the enormous economic power now wielded by the pharmaceutical industry over research, med-

ical education, and clinical practice. At the center of the story are the industry's attempts to exploit and extend patents on new brand-name drugs. These patents are one of the most lucrative forms of intellectual property in America today. This essay describes what happens when the drive to bring patented new drugs to market begins to control medical institutions and professionals who are supposed to be independent and unbiased.

The public agency responsible in the United States for overseeing the production and marketing of prescription drugs is the Food and Drug Administration (FDA). For most of its existence, the FDA has had the authority to regulate manufacturing standards and to require drug companies to prove the safety of their products.

In recent decades, the FDA has also usually required that the effectiveness of a newly patented drug be demonstrated in clinical trials, the results of which are submitted to the FDA and often published in peer-reviewed medical journals. Although some of the most important clinical trials are supported by the National Institutes of Health (NIH), the vast majority are sponsored by drug companies.

Marcia Angell, MD, is Senior Lecturer in the Department of Social Medicine at Harvard Medical School and a former editor in chief of the "New England Journal of Medicine." A predecessor in that post was Arnold S. Relman, MD, Professor Emeritus of Medicine and of Social Medicine at Harvard Medical School, who has been a Fellow of the American Academy since 1965. In the past two decades, Angell and Relman have played leading roles in criticizing the financial ties of medical researchers and academic institutions to the pharmaceutical industry.

In the year 2000, the pharmaceutical industry spent about \$3.77 billion on grants for clinical trials, compared with \$750 million spent by the federal government through the NIH. But even when a clinical trial is paid for by a drug company, the trial itself normally requires the participation of physicians and other experts. Many of these experts teach in academic medical centers, where the trials are designed and conducted. Increasingly, however, the researchers are doctors in private practice, who participate in clinical trials organized by private research companies.

The fact that investor-owned businesses sponsor most of the clinical trials that bring newly patented drugs to market presents multiple conflicts of interest for nearly everyone involved. That includes the drug companies themselves, whose essential business mission is to sell profitable drugs – not necessarily those that are optimally useful in medical treatments. It also includes the clinical investigators who receive funding from the companies to study the drugs, yet are supposed to be impartial, and the academic medical centers where much (but by no means all) of this work is done. Medical educators also find themselves with conflicts, since they receive industry support to conduct educational programs for doctors. And practitioners are constantly risking compromise by accepting the favors lavished on them by an industry determined to influence their professional judgment.

For millions of Americans, many of the drugs marketed by the pharmaceutical companies are essential for health, and even for life. Unlike most commodities, prescription drugs are often not optional goods. Furthermore, expenditures for drugs now account for the fastest-growing component of the national health

bill, and they will soon replace physicians' fees as the largest item on the bill, apart from the cost of hospitalizations. Prescription drug costs are a major and growing burden on individual patients and on public and private health insurers. As a result of these facts, the public has an interest in prescription drugs that it has in few, if any, other patented products.

Patents are the lifeblood of the drug industry. Without a patent, a company has no incentive to bring a drug to market. Patents, which are now usually granted for twenty years, give a company a monopoly that protects them from competitors as they develop the product and carry out the clinical trials necessary for FDA approval. Once approved, the drug can be sold on the market for the remaining lifetime of the patent, without risk of duplication by competitors. In addition, the effective patent life of many drugs is often extended by specific statutes and FDA regulations. The only price constraints – and they are weak – are those provided by a few competing companies with similar patented drugs and the pressures from large purchasers for bulk discounts. The theory behind patents and other forms of exclusivity is that they will provide an appropriate but limited incentive for companies to develop important and innovative new drugs. But, as we will explain later, the theory does not always work out in practice.

Most innovative drugs – that is, drugs that act in a different way from anything on the market – are now developed initially with NIH research funding, usually in academic medical centers. The drugs are then licensed to drug companies to be further developed and brought to market.

This subsidization of drug companies by the taxpayers became officially sanc-

tioned by Congress in 1980, when the Bayh-Dole Act was passed. Among other things, the Bayh-Dole Act (in conjunction with the lesser-known 1980 Stevenson-Wydler Act and several subsequent amendments) permits academic medical centers to patent drugs discovered through NIH-funded basic research. The academic centers are then permitted to license these drugs to private companies and receive royalties – which are shared with the investigators who conducted the research. The NIH itself is also permitted to set up collaborations with industry and to license drugs developed in its intramural program.

The ostensible purpose of the Bayh-Dole Act was to hasten the transfer of technology from government or academic laboratories to the marketplace. There was a general perception that the United States was lagging behind other parts of the world, especially Japan, in technology transfer. Whether that was true of the development of important new drugs is doubtful. The academic medical centers and their faculty nevertheless warmly embraced the Bayh-Dole Act – and so did the pharmaceutical industry.

Once public institutions had decided to join the drug companies in seeking patents whenever possible, little attention was paid to some of Bayh-Dole's constraints, particularly those that established the right of taxpayers to some sort of accountability, and also to some sort of return on their investment. Among these neglected provisions of the law was the requirement that the benefits of the "invention" be made "available to the public on reasonable terms." If that provision were violated, the law said, the government could "march in" and reassign the patent. The government also retained the rights to use the product itself. Some commentators have

interpreted this as a justification for some sort of price restrictions on drugs licensed to industry under the terms of Bayh-Dole. In addition, the research institutions were supposed to keep the government informed of all patents they obtained on NIH-funded work. Together, Bayh-Dole and Stevenson-Wydler contained provisions that would allow the public to recoup a portion of profits under certain limited circumstances.

In practice, virtually all of these provisions have been ignored or revoked. In 1995, the NIH itself advised against requiring "reasonable pricing," and in a report last year, it argued against trying to recoup a portion of profits. It emphasized that only four of forty-seven drugs with yearly sales above \$500 million were known to have been developed with NIH funding. What was not emphasized was the fact that there was no way of knowing about the other forty-three drugs, since the NIH had not required the medical centers to fulfill their obligation to supply information about patents they had obtained on taxpayer-funded work.

The chief effect of the Bayh-Dole Act has been to increase dramatically the number of partnerships between academic institutions and the pharmaceutical industry. There were many reasons why the drug industry wanted closer collaboration with medical institutions, but one was the need for companies to obtain human subjects for the clinical trials they needed to get FDA approval. Drug companies have money to support clinical research, but they don't have patients, so they need to look for them elsewhere. As the number of drugs being tested grows, so does the number of clinical trials, and human subjects are becoming increasingly difficult to find. Teaching hospitals are an important source, although no longer the only one.

Clinical trials have become a multibillion-dollar business, involving tens of thousands of investigators and millions of human subjects. There are now perhaps as many as sixty thousand ongoing clinical trials (no one knows the exact number).

Since companies usually sponsor trials only after they obtain patents, the time spent in trials eats directly into the time they have to market the drug with the protection of a patent. Consequently, the drug companies are in a great rush to get the trials done, and the rate-limiting factor is the difficulty in acquiring human subjects. In fact, to find subjects, drug companies routinely pay bounties to doctors – anywhere from \$500 to \$15,000 per subject enrolled – plus large bonuses for rapid enrollment.

Because the drug companies are in such a rush, they can no longer rely exclusively on academic medical centers to conduct the trials. They find they can get much faster service in the private sector. In just the past decade, the fraction of industry-sponsored trials done in academic medical centers has dropped from 80 percent to less than 40 percent. Many clinical trials are now organized instead by hundreds of for-profit companies, called contract research organizations (CROs). These companies often work with other companies that recruit human subjects through the media. CROs also organize community doctors to supply patients and collect data, or they work with still other satellite companies that do. These community doctors have become an army of amateur investigators. There are now about fifty thousand clinical investigators registered with the FDA, many of whom are community doctors involved in their first clinical trials.

Academic medical centers are trying to be more accommodating to drug

companies to win back the business being lost to CROs and other private research businesses. Conducting clinical trials for industry is a good source of revenue to help offset losses from low Medicare and managed care reimbursement. Some academic medical institutions are even setting up separate clinical research organizations to provide a convenient, single access point for drug companies and to provide them with the administrative services they need to deal with the FDA.

Many institutions are also permitting drug companies to attach strings to their grants that were unheard of just a few years ago. For example, in some arrangements with academic institutions, the companies may design their own trials, retain and analyze the data, write the papers or at least review them before publication, and even decide whether to allow publication at all. Under such conditions, investigators become little more than hired hands, and their institutions little more than drug company outposts. These are the abuses that provoked medical editors around the world to issue the announcement we mentioned at the start of this essay.

We have pointed out that many of the really innovative drugs are derived from NIH-funded research. For example, the anticancer drug Taxol was developed at Florida State University with NIH funds, then licensed to Bristol-Myers-Squibb. Indeed, nearly all of the major anti-cancer and anti-AIDS drugs were developed with the help of NIH funding.

What about the others? Nowadays, while some new drugs coming out of the pharmaceutical industry pipeline represent important new discoveries, most “new” drugs being developed by industry are not really new – they are simply variations on an existing theme. In fact,

the number of innovative drugs reaching the market has actually declined over the past several years, from a high of fifty-three per year in 1996 to twenty-seven in 2000.

At the same time, the market is being flooded with highly profitable drugs that usually belong to a family already on the market. For example, Claritin, one of the most profitable of all proprietary drugs, is simply one of a number of similar antihistamines used to treat allergies. Top-selling drugs like Claritin are often called “blockbusters,” and it is a revealing commentary on the pharmaceutical industry that most blockbusters are competing with several other, similar drugs that are also very profitable. Thus, the two blockbusters Zocor and Lipitor are members of a family of statins – drugs that lower blood cholesterol levels by inhibiting production of cholesterol in the liver. And the antidepressant blockbusters Zoloft and Paxil share a common mechanism of action with Prozac, itself a mega-blockbuster antidepressant that recently came off patent.

Drugs with similar actions (and frequently with similar or related chemical structures) are often referred to as “copycat” or “me-too” drugs. They are far easier to turn out than innovative drugs, although they require huge marketing campaigns to persuade doctors and patients to choose one over the other. In contrast, marketing costs for a truly groundbreaking drug, like a cure for cancer, would probably be small, because the drug would sell itself to physicians and the public – based on the published scientific evidence of its safety and effectiveness.

Marketing and administrative costs now equal roughly 30 percent of the revenues of the major drug companies, while research and development (R&D) amount to only 12 percent of revenues.

The profits of the drug companies also greatly exceed the money spent on R&D; on average, profits equal 19 percent of revenues.

The industry claims it spends \$500 million on each new drug brought to market, counting expenditures on failures. But most independent analysts believe that to be a highly inflated figure, and estimate the real figure to be closer to \$100 million. Regardless of what it is, the industry reaps huge profits. That fact would certainly seem to belie the contention of the drug companies that the high prices they charge are needed to offset the costs of their R&D.

A large share of the marketing budget of the pharmaceutical industry, about \$15 billion annually, is spent on wooing physicians in a variety of ways that cause serious conflicts of interest for the medical profession.

One of the principal ways is through educational programs. Physicians are required to obtain “continuing medical education” (CME) to renew their licenses. Increasingly, drug companies help fund and thereby influence these programs, which are usually sponsored by hospitals and medical schools. Physicians are often enticed to attend these CME programs with free meals and other favors and gifts. Drug companies also help professional societies with the expenses of scientific meetings, and they conduct their own satellite educational programs at those meetings. Most such meetings also feature commercial displays and eager salesmen pitching their company’s products. The problem with drug company involvement in CME is that sponsoring companies cannot be expected to evaluate their own drugs objectively, particularly in comparison with competitors’ drugs. Yet the impartial, comparative evaluation of drugs

should be an important function of CME programs.

Another expensive avenue by which drug companies seek to influence the prescribing practices of physicians is through what is called the “detailing” of practitioners in their private offices. This involves more than eighty thousand drug company representatives, who, at an annual cost of several billion dollars, visit doctors’ offices to tout their company’s drugs and to gain favor by plying doctors with free samples and other gifts.

Hoping to gain their share of a competitive market full of similar drugs, the drug companies find detailing to be an effective technique for influencing practitioners’ choices. But when doctors accept favors and receive information about drugs from company salespeople, they risk abdicating their responsibility to their patients, who have a right to assume that physicians will rely on their own interpretation of the best available information rather than on information supplied by necessarily biased drug companies.

Still another method used by drug companies to promote the prescribing of their top-selling drugs is to advertise directly to consumers in the popular media. In recent years, much money has been poured into an effort to persuade people to “ask your doctor about” a wide variety of drugs for common conditions. The medical information conveyed in these ads is fragmentary and sometimes misleading. The purpose, of course, is to increase popular awareness of a brand-name drug, which will then lead physicians to prescribe that brand in order to satisfy consumer demand. This practice fits well with the currently popular notion of “consumer-driven” health care, but it contributes little or nothing to the quality of medical services, and it cer-

tainly increases the costs of care.

Drug companies owe it to their investors to produce profitable drugs. But as the successful marketing of me-too drugs shows, a drug need not be especially medically useful to be profitable. In fact, one way to increase profitability is to market drugs for minor ailments aggressively. After all, there are more healthy people than seriously ill ones – at least in countries where people can afford to purchase expensive drugs. Therefore, an antihistamine or an agent that claims to help irritable bowel syndrome or one that dampens premenstrual mood swings has a much larger potential market than a drug for a serious illness.

A critical task for the drug companies is to obtain patents on me-too drugs or to extend patents on successful drugs. The drug companies accomplish this in a variety of ingenious ways. They try to find slightly new uses for old drugs or sell them in new combinations or dosage forms. Eli Lilly’s newly patented Sarafem is the same drug as Lilly’s Prozac, which has just gone off patent, but Sarafem is sold for premenstrual syndrome instead of depression. The antidiabetes drug Glucophage XR is Bristol-Myers-Squibb’s newly patented once-daily replacement for the twice-daily Glucophage, whose patent recently expired. Except for their duration of action, the two drugs are the same.

Two years ago, the *Wall Street Journal* reported a proposed complicated business deal between Merck and Schering-Plough for the marketing of two new drug combinations, one to lower serum lipid levels and the other to relieve allergies. Each combination would pair one company’s blockbuster drug, whose patent as a single product will soon expire, with a drug with supplementary

action owned by the other company. The combination drugs would have new patents, and their profits would be shared by both companies.

Not satisfied with twenty-year patents, the industry tries to extend them in other ways. The most direct but least certain way is to have a friendly member of Congress introduce a bill to extend the patent on a particular drug. Other methods are less direct but more effective. Thanks to a 1997 law, drug companies that agree to test their drugs in children automatically receive an extra six months of exclusivity – even if the drug would rarely be prescribed for children.

Companies also routinely file patents on some trivial feature of their brand-name drugs – for example, the shape of the tablets – and then sue a generic company for patent infringement when it is about to enter the market. The suit automatically extends the patent for another thirty months, or until the case is resolved. When patents finally do expire, according to allegations in several lawsuits filed by consumer groups, drug companies sometimes collude with generic companies to keep prices high.

In principle, both the FDA and the U.S. patent office have the power to prevent the kinds of abuses we have been describing – but in practice, neither agency exercises it. Over the past decade, the FDA has become increasingly friendly with the industry it regulates. Indeed, it sometimes seems as if the FDA views the drug companies, and not the American public, as its primary client.

There is some reason for that impression. In 1992, Congress passed the Prescription Drug User Fee Act. This act requires drug companies to pay a user fee – currently it is more than \$300,000 – to the FDA for every drug the agency reviews. Such fees at present constitute about half the budget of the FDA's drug review center.

The *quid pro quo* is simple: in return for the fees, the FDA reviews more drugs more quickly. Since 1992, the FDA has doubled the number of drugs reviewed annually, and cut in half the time spent on the average drug review. (In the past year or so, in the wake of several widely publicized withdrawals of drugs found to be dangerous, the FDA has slowed down a little.)

One can see from this brief overview of the clinical research system that it is permeated with financial conflicts of interest. Drug companies exert a major influence over the evaluation of their own products, either indirectly or directly, through for-profit organizations that are dependent on them. Yet the fiduciary responsibility of the drug companies is to increase the value of their stock. It is not to provide unbiased evaluations of their own products.

Even the nonprofit academic medical centers, now facing hard times in the managed care environment, are so eager for drug company business that they are ceding substantial control to the companies over the way academic research is conducted and reported. Researchers who run the clinical trials in academic centers are being allowed to enter into financial arrangements that compromise their independence. Meanwhile, most of the new, nonacademic researchers are private practitioners with no research experience who are paid large bounties and bonuses for enrolling their patients in trials.

Oversight of this situation falls, finally, to the FDA – an agency now partially supported by the industry it regulates. That support is precarious and almost certainly conditional on the agency's cooperation with industry. The Prescription Drug User Fee Act must be renewed by Congress every five years. But as the FDA well knows, the pharma-

ceutical industry has enormous clout on Capitol Hill. If the industry decided to withdraw its support for the Act, the budget of the FDA's drug review center would be slashed, and many people would lose their jobs.

These conflicts of interest are having exactly the effects on clinical research that might be predicted, and some of the consequences are worth emphasizing.

First, drug companies now broadly influence the kind of research being done. Drug companies are increasingly funding trials not to discover new agents and new approaches to treatment, but to get FDA approval of me-too drugs and to buttress marketing claims. For example, huge trials may be undertaken to show that a new statin is in some way marginally better than the other five already on the market. The research may result in successful marketing campaigns but is unlikely to yield much of any scientific or clinical value.

Second, there is growing evidence that financial conflicts of interest are compromising the integrity of the clinical research enterprise. As we have noted, drug companies now often control how and whether research is reported. Many clinical trials are never published because the results do not favor the sponsor's product. There have been several widely publicized cases of investigators who published negative results anyway and were harassed by their industry sponsors for doing so. For example, investigators in a recent trial of an HIV vaccine refused to allow the company to alter the report to make it more favorable to the vaccine. The company then tried to stop publication altogether. According to news reports, when the authors published anyway the company demanded \$7 to \$10 million in damages on the grounds that publication had hurt the company's financial prospects.

The publicized cases concern investigators who refused to tailor their results to suit their sponsors. More worrisome are the cases of investigators who quietly allow negative results to be suppressed, or who publish misleading work. Several studies have shown that papers with industry support are much more likely to favor the company's product than papers with NIH support. Bias may be extremely difficult to detect, particularly when it involves selecting only certain data to present. (Having exclusive control of the data, as drug companies often do, makes surreptitious selectivity all too easy.)

There is also evidence that human subjects are being enrolled in clinical trials for which they are not eligible – for example, because they do not have the disease in question. According to a recent Inspector General's report, physicians in one study stood to make a \$30,000 bonus when they enrolled their sixth patient. Under those circumstances, it's hard to imagine that eligibility criteria will not sometimes be stretched.

What we have, then, is a system riddled with abuses and conflicts of interest and badly in need of reform. How should it be changed?

First, we believe the Bayh-Dole Act should be enforced in all its original provisions, not just the ones that are lucrative for industry and academic institutions. Provisions that should be enforced include: 1) the stipulation that the government be notified of all patents obtained that are based on publicly funded research, and 2) the requirement that the fruits of the research be available to the public on reasonable terms. In the statute, the second provision is stated in only general terms, but it could be translated into specific regulations. Doing so

would help to ensure a reasonable *quid pro quo* between a protected and favored industry and the public that supports it and depends upon it for products essential for medical care.

Second, we recommend that full control of clinical research be restored to the medical institutions and the medical professionals responsible for the health and safety of the patients being studied. The FDA should not allow clinical trials to be controlled by for-profit businesses whose major or only clients are the drug companies. In other words, they should ban contract research organizations (CROs).

That would leave several alternatives. One would be to set up some sort of independent public agency that would function much as the CROs now do, but without having to compete for drug company business. Another alternative would be a return to the days when trials were mainly done in academic medical centers with arm's-length drug-company funding. In those days, academic investigators designed the trials, analyzed the results, wrote the papers, and published them no matter what the outcome. They had no other financial ties with the companies that funded the research, and neither did their institutions.

The academic medical centers should not have strayed from this model in the first place, despite their desire for drug company funding. In any case, FDA approval of new drugs should be contingent on assurances that investigators are not constrained by sponsors in the publication of study results and that they have no other financial ties to the sponsors. This would add strength to the new policy announced by the group of medical editors.

It will be protested that academic medical centers alone can no longer han-

dle the volume of industry-proposed clinical trials, and that is true. But that raises another issue. Is the volume of clinical trials now being undertaken by the pharmaceutical industry reasonable? Can we justify asking human subjects to participate in research that may be quite trivial?

One way to winnow out the trivial research is for the FDA to require that clinical trials, wherever feasible, compare the newly patented drug with the best existing one, not with a placebo. The FDA could also require that approval of a drug be contingent upon a clinically significant effect as well as a statistical one. For their part, the academic medical centers should not undertake clinical trials unless they have some scientific merit.

These reforms would cut down on the total number of clinical trials. They would encourage drug companies to concentrate their efforts on drugs of potentially significant medical value and not spend so much of their resources on the development of drugs with more commercial than medical promise. It is understandable that the industry should want to maximize its revenue, but not that a government agency or the academic medical centers should be its partners in this venture.

Third, Congress should increase the FDA's budget, to enable the agency to expand its responsibilities. The FDA should be shored up as a truly independent agency. It should not be permitted to continue down a road that will make it the captive of the drug industry.

Accordingly, the Prescription Drug User Fee Act should not be renewed in 2002. The FDA is, after all, a public agency charged with protecting the public health. The support it now receives through user fees should be replaced by public funds, and increased.

Fourth, we think that the terms of the collaboration between academic medicine and the pharmaceutical industry need to be reevaluated. Academia and the drug industry can serve the public interest well when they collaborate in research, but only when they do so under arrangements that keep their separate missions distinct and do not encourage academic institutions or their faculties to go into partnership with the companies or to become businesses themselves.

We believe that all financial ties between clinical investigators and the companies whose products they are testing for clinical use should be prohibited – either by law, or through the joint policies of academic medical centers. The only remedy proposed so far has been disclosure – to the institutions, to human subjects, and/or to the editors and readers of medical journals. But disclosure will no longer suffice. The pervasiveness and influence of these financial associations, and the scope of the public's stake in the matter, demand stronger action. We are convinced that the time has come simply to eliminate all such conflicts of interest.

Fifth, and finally, we think it is time to separate continuing medical education (CME) from the marketing of drugs. The former is the responsibility of independent educational institutions; the latter is the legitimate province of industry. The drug industry should not encroach on the intellectual independence of the medical profession – even if this means that physicians have to assume more of the financial burden of their own continuing education.

But the primary responsibility for reforming the current troubled state of CME clearly lies with the medical profession. The medical schools, the hospitals, and the professional organizations that ought to be responsible for the education of physicians should simply refuse financial help from the pharmaceutical industry, unless it is totally free of any industry participation.

We need to remember that the missions of the drug companies and of academic medicine, while in some respects complementary, are in most respects quite different. The primary mission of the pharmaceutical industry is to make money by developing, patenting, and then selling safe and effective drugs. The best of these drugs may make an important contribution to medical care.

The mission of academic medical centers, which are almost all nonprofit, is to educate physicians, advance medical knowledge through basic and clinical research, and provide clinical care of the highest quality.

Industry and the academic centers can sometimes collaborate very fruitfully in research leading to the development of new drugs. But if they wish to preserve the public's trust, and if the centers want public support, they should avoid financial arrangements that blur the essential distinctions between their separate missions. Unfortunately, competitive pressures in the health-care system and the lure of huge profits from pharmaceutical patents are causing industry and the academy to ignore this caution – with potentially grave implications for the public good.