

## HOW CONFLICT-OF-INTEREST RULES ENDANGER MEDICAL PROGRESS AND CURES

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An active partnership between science and commerce underlies Americans' high standard of living, including their state of health and the medical discoveries and treatments that have steadily improved it. But a mounting wariness toward collaborations between employees of research institutions and public agencies and those working for pharmaceutical companies and the like, as expressed in increasingly broad conflict-of-interest rules and prohibitions, threatens to disrupt what has been a wide-ranging and productive exchange of knowledge and information. Populist in its objection to scientists' enrichment and puritanical in its belief in money's certain corruptive powers, this new regulatory philosophy is likely to degrade the quality of research and delay the provision of lifesaving medicines and treatments.

Without carefully weighing the impact of such harms,

- The National Institutes of Health has forbidden almost all contact between its scientists and those in the private sector. Yet an industry scientist may be the world expert in an NIH scientist's area of research, and others could facilitate the translation of basic research into useful technologies, which is supposed to be one of the agency's goals.
- The Food and Drug Administration has started demanding extensive public disclosure of the financial ties and payments of experts appointed to committees that review the licensing of new drugs and their accompanying warnings, an encroachment on their privacy they are sure to find distasteful. It does so despite the fact that a third of these positions are unfilled.
- Universities have become leery of cooperation with drug companies out of concern to preserve the single-mindedness of pure research. Yet they do not hesitate to patent fee-producing devices invented in their laboratories with federal financial assistance, as 1980's Bayh-Dole Act permits them to do.
- The parent organization of two Harvard-affiliated hospitals has placed strict limits on per diem compensation for service on corporate boards, which only encourages physicians to devote more time to activities beyond their hospital duties.
- Leading medical societies are considering whether to prohibit their physician members from accepting fees from drug companies to inform medical audiences about medicines the companies are marketing. Yet such presentations occur before informed, professionally skeptical audiences that may contain representatives of competitors well-equipped to contradict false or misleading claims.
- Massachusetts has enacted the Pharmaceutical and Medical Device Manufacturer Conduct Act, which imposes a sweeping prohibition against gifts, including training sessions, from such businesses. The net effect, however, will be to move such valuable activities beyond the state's borders.

Such censoriousness rests on at least two questionable assumptions; first, that parties with some kind of financial interest, however trivial, are, inevitably, purveyors of bad information; and second, that reliance on information from such sources, or even on information that is actually bad, is worse than an absolute reduction in the amount of available information, which occurs when industry sources are closed off.

Except in egregious cases, conflicts of interest are a necessary part of doing business in an interconnected world. These conflicts can be managed through a judicious combination of disclosure and oversight. Severe and broad conflict-of-interest regimes sweep before them even highly regarded, well-motivated professionals, denying society the benefits of the knowledge they possess.

## ABOUT THE AUTHOR

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RICHARD A. EPSTEIN is a Manhattan Institute visiting scholar and one of the nation's most prolific legal thinkers. Epstein's writings span a broad array of fields, from the common-law subjects of property, contracts, and torts to constitutional law and law and economics. He is the author of numerous books, including *Simple Rules for a Complex World* (Harvard University Press, 1995) and *Takings: Private Property and the Power of Eminent Domain* (Harvard University Press, 1985). He has written extensively on American health care, most recently in *Overdose: How Excessive Government Regulation Stifles Pharmaceutical Innovation* (Yale University Press, 2006), and earlier in *Mortal Peril: Our Inalienable Right to Health Care?* (Addison-Wesley, 1997). He is a columnist for Forbes.com, and a contributor to *The Wall Street Journal* and *The New York Times*. Epstein was appointed the Laurence A. Tisch Professor of Law at New York University School of Law in 2010. He will continue to serve as the James Parker Hall Distinguished Service Professor of Law at the University of Chicago, where he has taught since 1972, until January 1, 2011, at which time he will become a lecturer there. In 1983 he became a senior fellow of that institution's MacLean Center for Clinical Medical Ethics. At the University of Chicago he edited both the *Journal of Legal Studies* and the *Journal of Law and Economics*. He has also been, since 2000, the Peter and Kirstin Bedford Senior Fellow at the Hoover Institution. Epstein holds undergraduate degrees from Columbia College and Oxford University and a law degree from Yale. He was awarded an honorary doctorate of law by Ghent University, in Belgium.

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## INTRODUCTION: TOO MUCH, TOO SOON

In virtually every line of business and professional life, individuals are forced to make decisions in which their personal interest is in conflict with duties of loyalty owed to other individuals. Corporate officers and trustees owe duties of care to their shareholders and beneficiaries, respectively. Lawyers owe duties of loyalty to their clients. Agents owe duties of loyalty with respect to their clients. Employees owe similar duties to their employers. And, of course, physicians owe duties of loyalty to their patients.

For very long periods of time, an insistent set of social norms supplied the main incentive for persons in positions of trust to discharge their duties. The body of law dealing with these issues was never small; but it was never all-pervasive. In the areas of medicine and drug development, for example, the law books always contained scattered judicial decisions and administrative regulations that tackled the conflict-of-interest problem. But it is only in the last generation or so that the regulation of conflicts of interest has turned into a regulatory growth area.

Without question, this development has been sparked by widespread public uneasiness and distrust of individuals in places of power. It is partly driven by revelations of supposed misconduct by persons in high places. And it is partly carried along by sentiments

that have strongly favored government regulation of virtually every area of life. The size of the output in biomedical areas alone is staggering. Virtually every week, another article or book denounces shoddy practices in scientific research. The adoption of new codes to regulate conflicts of interest proceeds at fever pitch and is often followed by pleas for the fundamental restructuring of some major segment of American life to meet the dire threats that have just been isolated.

I make no secret of my uneasiness with this recent regulatory expansion, which deploys expensive administrative sanctions to create dubious incentives for efficient conduct, both in government regulators and the private parties whom they regulate.<sup>1</sup> In light of its often perverse consequences, this new regulatory apparatus should not be left unchallenged. In this essay, I want to go against the grain by attacking the modern reaction against the many inevitable conflicts of interest that arise in the research, development, production, and marketing of pharmaceutical products. This issue is, of course, not limited to the industry so engaged. It arises as well in any field where dual loyalties may generate unfortunate outcomes by conscious choice, willful indifference, or mere inattention. But given the huge cloud of suspicion that hangs over the pharmaceutical and medical-device industries, this concern has generated a host of intrusive and unwise policies and injunctions that throw sand into the gears of progress at every stage of the drug production cycle, from basic research through final sale.

I shall begin in Part I with a brief account of what counts as a conflict of interest in medicine and elsewhere in order to explain why conflicts of interest always raise inescapable and thorny issues of social control for private groups and government agencies. Yet the brute fact that *some* form of regulation is appropriate does not indicate *which* form of regulation should be adopted. Accordingly, Part II explores the choice between ex-ante and ex-post forms of regulation to see which type of regulation or, more precisely, what mix of regulations minimizes the sum of both kinds of regulatory errors: excessive oversight and lax oversight. Once the proper balance is explained, I examine the types of new regulations that are now being imposed

upon government and private employees. In Part III, I address the conflicts of interest in government work, focusing on the National Institutes of Health and the U.S. Food and Drug Administration. Part IV examines the conflict-of-interest regulations that deal with the relationships between university and industry. Part V turns from research and development to address the conflict-of-interest regulations governing the marketing of new pharmaceutical products and medical devices to the medical profession.

In all contexts, ever more stringent regulation has long passed the point where it does some good in controlling conflict-of-interest abuses. Regulations have now advanced to the point where they are far more likely to drive out of key positions the very individuals whose expertise and judgment are needed to make the delicate decisions that could determine the success or failure of a given program. The current conflict rules that are ordered by such key organizations as the NIH, the FDA, and various medical schools and medical societies have passed the point of good sense and have entered an area where we can predict serious difficulties. It cannot be wise, for example, for the FDA to announce exhaustive new disclosure policies for members who sit on its review committees at a time when about 215 of the more than 600 seats on the forty-nine FDA advisory committees are now vacant.

The defenders of the new regime of womb-to-tomb conflict-of-interest regulation know that the stakes are high. Necessarily all matters concerning the research and development and commercialization of drugs give rise to life-and-death questions. Test and promote the wrong drug, and its side effects can easily create incalculable levels of harm; prescribe the right drug to the wrong person, and a similar fate awaits. Sell a new and expensive drug when a cheaper and established drug will do, and a strapped health-care system will go further into hock because third-party providers pay premium prices when cheaper products are available.

But the flip side is equally important. Stifle the marketing and promotion of new drugs that outperform their rivals, and their tardy arrival could spell death or

serious injury to the people who cannot obtain the desired relief from existing drugs. Both kinds of error matter, and any effort to frame conflict-of-interest policy only with reference to the first will lead to serious errors, precisely because that second risk is overlooked or minimized.

Indeed, even when that second risk is taken into account, it is often understated. The simple point here is that the additional costs to the manufacturer of new drugs and medical devices are only a small fraction of the total social losses that are attributable to delay. The major component of the losses is often the foregone consumer surplus, which is, at a minimum, the difference between the maximum amount that informed consumers would pay for the product and its cost. In reality, as Tomas Philipson and Eric Sun have recently demonstrated, the additional costs of delay to a firm could easily amount to many millions of dollars.<sup>2</sup> By the same token, successful versions of these drugs generate billions of dollars in consumer surplus to the millions of individuals whom they serve. No one could claim that all the recent delays in drug approval stem from the added barriers imposed by conflict-of-interest regulation. The length of clinical trials, the FDA's fabled attitude toward risk, and a dozen other factors play some role in the overall process. But even after those factors are taken into account, it would be a mistake to ignore the long-term effects of conflict-of-interest regulations. The errors from delay are not just industry issues: they are also social issues.

At this point, we should cast a skeptical eye on the zeal that propels concerned citizens and policymakers to undertake new regulatory initiatives. It is common to justify a new round of restrictions at every phase of pharmaceutical and device regulation with the war cry "Better safe than sorry." That maxim works well in explaining why ships should stay in port when visibility is poor, the wind is high, and the terrain is unknown. But this image does not carry over to issues of pharmaceutical research, where regulations routinely deny even prudent individuals and firms a "safe harbor," where they can collaborate without fear of sanction.

The cause of the growth in restrictive regulation is not hard to find: high-profile scandals at leading companies

and research institutions. But the decision to impose additional obstacles in the path of new drug marketing and development is always highly risky, especially to persons with dangerous conditions for which there are no known acceptable therapies and treatments. In these circumstances, the speed with which needed new products get to market depends critically on the institutional arrangements that guide their movement from initial conception to ultimate commercialization. The relevant processes are never in the control of a single individual, let alone a single firm.

In modern business environments, the success of product development is therefore a function of both the speed and soundness of information transfer up and down the chain of production. Alas, these twin imperatives—speed and reliability—necessarily work at cross-purposes. Excessive speed may lead to shoddy results. Excessive care, however, may prevent sick people from getting much needed treatment in timely fashion. The trade-off between speed and soundness is endemic to all social-production cycles. Controlling these simultaneously depends critically on developing close connections among all individuals in the production cycle so that the insights learned at one stage can be made available to people working at either a previous or subsequent stage.

The adoption of aggressive conflict-of-interest regulation can exert deleterious effects on both aspects of information transfer. In contrast, modest systems of conflict regulation can improve reliability while causing relatively little dislocation. Regrettably, the ever greater suspicion of collaboration and cooperation has placed unnecessary bumps in the road to sound product development and commercialization. This essay is meant to expose the pitfalls of overregulation.

## PART I: DEFINITION OF "CONFLICT OF INTEREST"

**T**he standard concern with a conflict of interest arises out of the general loyalty that an individual in a position of trust owes to someone else. It is widely understood that all people tend to act in their individual self-interest. In an arm's-

length relationship between strangers, it makes good sense for each person to bargain as hard as he or she can, as each side can count on the other to take care of its own interest. But in many fiduciary situations, people trust others to look out for their own interest. Thus a patient trusts his physician to make decisions on health care and treatment that benefit the patient and that do not instead serve some grand academic research agenda.

Similarly, when individuals sit on boards of corporations and charities, their actions should be directed toward the welfare of the organization that they represent, which makes it improper for them to steer the deals of their organization to particular groups in which they hold an undisclosed financial or personal interest. Quite simply, the willingness to serve two masters at the same time unavoidably puts individuals into delicate conflict-of-interest situations.

The issue of conflict of interest has increasingly been a key element of policy for all sorts of organizations. Harvard Medical School, for example, defines a conflict of interest thus: “A Faculty Member is considered to have a conflict of interest when he/she, any of his/her Family, or any Associated Entity possesses a Financial Interest in an activity which involves his/her responsibilities as a member of the Faculty of Medicine. Included in these responsibilities are all activities in which the Faculty Member is engaged in the areas of teaching, research, patient care and administration.”<sup>3</sup>

It is equally common for charitable organizations as well as business corporations to develop conflict-of-interest guidelines that correspond to those at issue here.<sup>4</sup>

## PART II: REGULATION EX ANTE VERSUS REGULATION EX POST

Let us begin with a general account of the appropriate use of conflict-of-interest regulations to promote the sound transmission of information. To understand how these regulations should operate, it is necessary to articulate the connection between regulatory schemes that intervene before something improper occurs and those sanctions that are triggered

only by the occurrence of some wrongful action, be it taking bribes, fudging data, or leaking trade secrets.

The difference in incidence between these two strategies requires discussion. Those regulations that operate prior to the commission of any wrongdoing necessarily strike at good and bad actors alike. Using these sanctions, when properly conceived, has the obvious advantage of tending to prevent the messy scandals that arise after some wrongful act takes place, often with unanticipated and very disruptive effects.<sup>5</sup> But at the same time, the intrusiveness of these sanctions imposes heavy costs on projects that, in the fullness of time, could be completed with no adverse consequences. In the law, “justice delayed is justice denied” goes the adage. When conflict-of-interest rules are applied to medical research, the price can be both medical care delayed and medical care denied. The stakes are high, for delay can easily lead to death for people clinging to life. The cumulative costs of delay should be taken into account in thinking about each stage of drug design, testing, and commercialization.

There is no pat answer for how to mix ex-ante remedies with ex-post ones. To improve performance generally, the best way to resolve this remedial trade-off is to make the two types of remedies work, wherever possible, in synergistic fashion. Often, that approach requires a system of using a set of widely circulated and highly publicized announcements to warn individuals of the adverse consequences of conflicts of interest, should they materialize. Forewarned is forearmed. That one cheap remedy today can easily prevent many a conflict of interest from rearing its head tomorrow. In making this maneuver, it is advisable to select the key wrongs that merit special attention.

It is a bad idea to list thousands of potential violations because then no one can be certain which matters count and which do not. Clutter degrades the power of any key signal. It is better to follow a simple program calling for the release of all experimental data and the disclosure of all funding sources. That conclusion is drawn from the law of product warnings, where a few clear cautions about main risks outperform multiple, obscure warnings, all of which are likely to be disregarded. The ten-page FDA package insert

that lists all side effects regardless of probability does less well than the simple pharmacist's label on a prescription container that reminds users to take the medication with plenty of water, or instructs them not to drink grapefruit juice within four hours of doing so. Simple remedies for complex processes should never be disparaged when they actually alter behavior for the better.

The second set of anticipatory remedies often required has more bite. Individuals must make key disclosures of financial conflicts to relevant authorities, who are then in a position to guard against possible abuse. At that point, the central oversight committee could decide whether a principal investigator may continue working on a particular project and, if so, subject to what conditions. The key issue here is how freely the authorities should grant waivers to participate. Until recently, for example, the FDA was relatively liberal in granting waivers. But more recently, it has taken a much harder line, with predictable results: fewer good people to sit on these committees.<sup>6</sup>

Undoubtedly, at all key levels, the willingness of governing authorities to issue waivers has diminished markedly, almost ensuring that disclosure of a potential conflict of interest will lead to exclusion from participation in key projects.

I have no doubt that the severity of any anticipated conflict of interest matters. Conflicts should sometimes lead to disqualification, but not always. Strict separation of operating units as a solution to the conflict-of-interest problem runs the high cost of impeding or even stopping the orderly transfer of information among experts at all points in any complex distribution system. The substitute lines of exchange could easily be less open, and they, too, could be blocked out of excessive fear of yet other conflicts of interest. If a government or private body adopts the ban-first, think-later approach, all formal and informal means of communication could effectively be blocked.

At this point, the following rough generalization holds. A total ban on particular persons should be invoked only when alternative modes of communication and investigation are abundant and secure. In cases where

only imperfect substitutes are available, continued participation in a given venture should be encouraged, subject to various forms of cooperation, supervision, and oversight by persons who do not labor under the same direct conflict of interest. Finally, in high-frequency/low-level interactions, such as the mass promotion of new products, disclosure itself to the intended audience may be all that is required, with the possibility always held open that if a party engages in improper conduct after the disclosures are made, additional targeted sanctions could then be imposed.

This system of disclosure, followed when necessary by specific remedies, is far less intrusive than current strategies that insist on total separation for a very broad range of conflicts of interest. That contemporary one-two punch—adopt a broad definition of a conflict of interest, and then impose stiff sanctions for a violation of the conflict-of-interest rules—can block the easy flow of information needed at every stage in the drug-development process.

To show how these differential remedial strategies play out, it is necessary to look at each link in the development process, which starts with basic research in scientific laboratories and at the National Institutes of Health, and works its way through the development of new drug products within the pharmaceutical industry. These products must then be patented and subjected to clinical trials before commercialization to the medical profession and the public at large can occur. Even then, the cycle of information transfer is not complete because post-sale evaluation of most products can provide valuable information on their performance and side effects that short clinical trials with smaller populations cannot provide.

The new trend in conflict-of-interest regulations pushes in the wrong direction at key stages of the drug-production cycle. To show how the entire situation plays out, I shall start with an examination of the conflict-of-interest regulations promulgated by the National Institutes of Health in 2005. I shall then discuss the new conflict-of-interest policies that have been adopted by the FDA. Then I shall turn to connections between universities and pharmaceutical companies.

## PART III: CONFLICTS OF INTEREST IN GOVERNMENT WORK

### National Institutes of Health Regulation

The current NIH regulations were promulgated in February 2005. As is often the case, these tough guidelines, which interdict virtually all cooperation with scientists in the for-profit sector,<sup>7</sup> followed a whiff of scandal arising from certain aspects of the NIH's far-flung operations. In the mid-1990s, Harold Varmus, who was director of the NIH from 1993 to 1999, lifted all restrictions on the amount of income that senior NIH scientists could collect from their outside consulting work.<sup>8</sup> His very lax attitude toward consulting produced the predictable uproar when it was discovered that one NIH medical researcher during that time had published an article that praised Crestor, an AstraZeneca drug used to control cholesterol, without mentioning its known safety problems or his consulting payments.<sup>9</sup>

Around the same time, another physician failed to disclose \$285,000 in consulting fees that he received from Pfizer (the company made proper disclosure of the payment) while working on patient responses to Alzheimer's disease for both Pfizer and the NIH. The risk of favoritism toward Pfizer is evident in principle—although in the particulars of this case, no such favoritism seemed to be present.<sup>10</sup> Where there is smoke, there need not be fire.

Any sensible set of disclosure obligations would have caught these two particular actions. The proper response is to throw the book at anyone who consciously conceals known adverse side effects in any published study—paid or unpaid. The only open question relates to the proper sanction for this undoubted form of scientific misconduct. Does it amount to academic fraud or inexcusable neglect? The prompt application of existing NIH (and journal) sanctions should have been sufficient to cover this situation.

The second case is just as easy. Full and prompt disclosure of a major conflict of interest in work done for pay at Pfizer was required under the NIH procedures then in place. Had those disclosures

been made, an informed judgment could have been reached on whether to stop or limit the collaboration, which—ironically, in this case—may well have gone forward. The further charge of favoritism toward a paid client obviously requires an investigation, even though, as noted, Pfizer was innocent of any and all wrongdoing.

Even if we adopt the worst-case scenario in both cases, it is important to keep these incidents in perspective. The NIH is a huge organization, with 6,000 research scientists and an annual budget in the billions of dollars.<sup>11</sup> Serious lapses in judgment by two individuals, however inexcusable, do not suggest a serious institutional breakdown in the applicable scientific norms. Further revelations that about 100 other senior scientists did not file the required forms does hint at some systematic varieties of lax administrative oversight, even if some or most of the violations were only technical. But these incidents, even when taken together, do not suggest a need for new rules to plug the gap. They suggest only that the rules already on the books should be diligently enforced. As a matter of first principle, the disclosure of relevant contacts is needed to decide which collaborations should be allowed, and on what terms.

The new NIH regulations were, from every point of view, senseless overkill intended to stave off a strong political response from Congress, which was eager to demonstrate that it remained an effective guardian of public funds.<sup>12</sup> The new regulations start with a clearly laudable policy goal: “The public must be assured that research decisions made at the NIH are based on scientific evidence and not by inappropriate influences.” The regulations are also correct in their further assertion that “senior management and people who play an important role in research decisions must meet a higher standard of disclosure and divestiture than people who are not decision-makers.”

### Divestiture

Before turning to the disclosure issue, it is worth mentioning the requirement that senior scientists and administrators divest themselves of holdings in private companies. Often it is easier for administrators to

formulate these edicts than it is for research scientists to carry them out, especially since the prohibition in question applies not only to NIH scientists but also to their spouses. The problem can raise difficulties in recruitment if potential NIH scientists have shares in private corporations that are not readily marketable before the development cycle has run its course. To force a bargain-basement sale would be most unwise. To insist that the employee or spouse give up work in the area of specialization poses risks as well.

In general, scientists will have the same incentives that they had before they joined the program to establish the soundness and commercial potential of their products. Allowing people to continue with their research under supervision would seem to be an adequate remedy, at least until options can be exercised or until restricted stock can be sold in the open market. Here again, it is never possible to be certain about how these issues should be handled in the abstract. But there was an ample track record compiled by these dual interests before the invocation of the new regulations. It is unexplained where these regulations broke down. Clearly, the incremental approach that seeks to correct past failures will do far better than an alternative approach that lurches without clear justification from one extreme to the other.

### Communication and Collaboration

Although the question of divestiture may cover only a small fraction of cases, the issue of disclosure applies to all research scientists. Yet the strict separation that prevents conflicts of interest also prevents cooperation. The question is how the two goals operate in tandem, when neither can be considered in isolation. Collaboration—formal and informal, local and international—is vital to academic success. Any sound institution will encourage scientific interactions to facilitate the cross-pollination of ideas with outside scientists. Many of these potential exchanges do not pose the slightest risk of inappropriate influence. Nonetheless, the NIH regulations go overboard in an effort to establish their own probity. Their first error is one of omission, not commission. The NIH's third basic guideline rightly speaks of the need for further interaction with persons outside the NIH: "To

advance the science and stay on the cutting edge of research, NIH employees must be allowed interaction with professional associations, participation in public health activities, and genuine teaching opportunities." The key players omitted from this list are scientists at pharmaceutical companies, large or small, whose applied research could be expedited by contact with the NIH's basic scientists. Yet it appears that those connections, however fragmentary, are subject to an NIH de facto ban even if done without pay. After all, what NIH scientist wants to be hauled before Congress for speaking to a scientist working on a compound on which the industry scientist is a world expert?

The discontinuities are even more pronounced because the NIH runs its own Office of Technology Transfer,<sup>13</sup> which follows a licensing strategy to reach its social objectives: "to ensure development of each technology for the broadest possible applications, optimizing the number of products developed from NIH technology." It then expresses a preference for nonexclusive licenses as the most effective way to get its patented technologies and products out into the public space. In this regard, the modern policy is consistent with the sensible approach to patents urged by Vannevar Bush (who headed the United States science effort during World War II) in his 1945 Report to the President, "Science The Endless Frontier." Bush pronounced the system as basically sound but in need of some clarification<sup>14</sup> and thought that the various Institute heads should have broad discretion in setting patent policy.<sup>15</sup> The permissible options include various forms of licensing as well as placing the results of NIH research squarely in the public domain.

The details of this patent policy are not the key point here, however. What matters is that the current NIH conflict-of-interest policy works at cross-purposes to the NIH's long-standing outward-looking licensing policy. Nonexclusive royalty licenses and open public licenses will work better if the licensing of intellectual property is accompanied by an orderly transmission of information about how NIH technology and products work. Most private licensing agreements are not restricted to a simple technology transfer. They often involve the sharing of new information that proves advantageous to the other side of the licensing arrangement.

It seems a bad trade-off that a hypothetical risk of some conflict of interest should place heavy barriers in the path of fruitful collaborations between basic scientists and their counterparts in private industry. The restrictions will impede the willingness of outsiders to license from the NIH and will reduce the price that they are willing to pay for any license, all of which is bound to have a negative impact on the operations as a whole, including companies' capacity to expand their research base.

The clear bias against industry is also reflected in the NIH's efforts to clamp down on other forms of collaboration between industry and basic scientists. The guidelines deem participation by NIH scientists in public health activities and genuine teaching opportunities to be acceptable. But do public health activities include work done by private for-profit firms on vaccines capable of controlling major public health risks? And would cooperative work with Merck on its vaccines program fall within this exception? I suspect not. Even if some obscure NIH regulation let such a collaboration pass muster, it won't happen. In light of the manifest drift of the regulation, what individual scientist would want to go through the NIH prior-approval policy for working with industry?

The reference to "genuine" teaching opportunities also contains a clear negative implication. Speaking for pay, or even without pay, to the research group of a major drug company does not sound as though it meets this requirement of genuineness. How it affects participation at open meetings where industry and NIH scientists interact is hard to say. But the manifest weight of this one regulation is sure to cast a pall over all sorts of interactions that matter.

A wholesale revision of the basic policy is needed. It is critical that the NIH treat collaboration as the main objective and conflicts of interest simply as an important side constraint. The NIH should seek not only to remove barriers to cooperation but to open additional possibilities to it by sponsoring workshops and conferences that bring together scientists from government and universities to work together on joint projects whenever possible. It should develop a sensible conflict-of-commitment policy—one day per week is the norm—that allows for consulting, subject

to constraints on the nature of the subject matter. The instincts of Vannevar Bush were far sounder on this matter than the current ethos, which places suspicion above cooperation.<sup>16</sup>

## FDA Conflict-of-Interest Regulation

The treatment of conflict-of-interest issues is also of key importance to the work of the FDA, which oversees the government's licensing of new drugs and their accompanying warnings. That work necessarily involves much specialized expertise that cannot be found within the ranks of the FDA. Therefore it is routine practice for the FDA to assemble a range of expert advisory committees, forty-nine in all,<sup>17</sup> to review key submissions of the various drug companies. Within the FDA, responsibility is delegated to the Center for Drug Evaluation and Research (CDER).<sup>18</sup> In dealing with these issues, the traditional approach at FDA was to go light on the conflict of interest in order to attract the best minds to the committees in question. As late as October 2006, John Calfee of the American Enterprise Institute gave this assessment of the then-dominant FDA practice: "When asked over and over again why it does this, the FDA always replies that the search for the very best pharmaceutical research scholars inevitably turns up numerous conflicted researchers because pharmaceutical firms also want to obtain the best possible expert advice. Eliminate conflicted researchers, and you tend to eliminate the most valuable adcom members."<sup>19</sup>

In this setting, protecting against conflict of interest is accomplished by a variety of informal methods. Because committee members closely interact, they risk a rapid loss of reputation if they show bias. Committee members will back out of deliberations when their own products are being considered and usually when a product in direct competition is being reviewed. In most cases, good staff work presents the issues in relatively clear fashion, producing a consensus decision whether to reject, ask for more information, or approve.

In dealing with these questions, it is difficult to get a handle on the actual level of bias that is found. One study, written by researchers at Public Citizen, no friend of industry, examined 221 meetings of sixteen

FDA advisory committees. The upshot was a very high rate—73 percent—of meetings in which one or more key scientific advisors or consultants were present. Yet the number of recusals was quite small, about 1 percent. Participants' financial interests of various sorts were in the range of \$10,000 to \$100,000, which is above the standard thresholds today. Yet the impact on overall outcomes was small: "In all 3 conflict categories, the exclusion of advisory committee members and voting consultants with conflicts would have produced margins less favorable to the index drug in the majority of meetings, but this would not have changed whether the majority favored or opposed the drug."<sup>20</sup> From these data, it could be concluded that the conflicts have some modest effect. In principle, modest effects at most require modest adjustments to practices, which will result from a greater alertness to the difficulties of the situation. But given the overall pattern of behavior, the only conclusion that makes sense is that the set of reputational and institutional sanctions that Calfee identified has worked well.

Nonetheless, the absence of any smoking gun indicating the dangers of current practices has not prevented a sea change in social policy, driven by a powerful consensus in the academic literature on the question. Thus a strong call for conflict-of-interest regulation was found in *JAMA* shortly before publication of the Public Citizen study, which relied on the claim that "[t]he systematic review of the medical literature on gifting by Wazana found that an overwhelming majority of interactions had negative results on clinical care."<sup>21</sup> In fact, the Wazana study made no such extravagant claim, concluding only that "the present extent of physician-industry interactions appears to affect prescribing and professional behavior and should be further addressed at the level of policy and education."<sup>22</sup> As has been pointed out, noting differences in apparent patterns of behavior is a far cry from presenting evidence of any newly found dangers in physician care.<sup>23</sup> Nonetheless, in a spirit of a priori anxiety, the FDA began to tighten its policy in response to academic warnings of runaway conflicts of interest. Unfortunately, the consequences are just what one would predict.

As of June 1, 2010, there were many vacancies on key FDA committees: an examination of the FDA website on

this point revealed sixty-four vacancies on the various Drug Products committees: eighty-five on the various Medical Devices committees; thirty-three on the various Blood, Vaccines and Biological Products committees; and eight on the various Science Board to the FDA, Risk Communication, and Pediatrics committees.<sup>24</sup> On the forty-nine committees, about a third of the seats were empty, representing more than 200 members. It would therefore seem that the first priority should be to fill seats and not to place additional obstacles in the path of that objective. Nonetheless, in March 2010, the FDA moved in a more restrictive direction when it issued a report that tightened the disclosure requirements that candidates needed to meet in order to participate on these committees.<sup>25</sup>

The FDA engages in studied ambiguity to avoid any serious judicial review of its determinations, which it announces as "mere" guidelines, albeit guidelines that will be enforced with commendable zeal unless waived. The special government employees (SGEs), as these committee members are called, are now subject to extensive screening, which has the effect of driving many of the most qualified of them out of the system. Waivers are issued only "after close scrutiny" but not public disclosure of the private connections. The new twist to the regulations is to require public disclosure by all SGEs of "the type, nature, and magnitude of any waived financial interests" of the SGE and relevant family members. The only exception to this policy, of uncertain scope, deals with information that is exempt under the Freedom of Information Act or that relates to a "company's confidential commercial information." Each such disclosure requires not only the nature of the connections but, within particular ranges, their dollar value, to be stated, and the full disclosures will be reported on the FDA website for all to see.

What is so striking about this departure is the lack of any sustained study of its multiple effects, or even acknowledgment of the Public Citizen study cited above. Rather, the FDA contents itself with abstract generalizations that claim, without empirical support, that the newer disclosure requirements will contribute to the "transparency, consistency, and clarity of the advisory committee process," as if that were the sole end of conflict-of-interest regulation. Whether these guidelines could deter the participation of many

successful scientists who do not wish to have their personal life history spread before the government is not explicitly considered in the report. Nor is there any reasoned effort to explain what additional benefits are gained from listing all this information. Most members of the public would be content to trust the FDA itself to make a judgment as to who should serve on these committees.

It is highly doubtful that any of the information gathered will be used by the public to evaluate these services; it is more likely to be used by all sorts of people for purposes that have little or nothing to do with the ends of the study. As a lawyer who frequently consults (but never for the government), I would not take any job that required disclosure of this information, and I expect that many distinguished medical personnel feel the same way. Disclosure that the FDA makes to the public is light years away from the disclosure that any panel member makes to the FDA. In view of the number of vacancies on these key committees, the likely result of this maneuver will be to narrow the pool of qualified applicants. The likely outcome is additional delay, weaker committees, and more dubious decisions.

How this counts as a blow on behalf of public health is not apparent. The FDA is insistent that all its actions are always intended to protect the public from the various perils that it faces. But the FDA never once considers whether its own actions add to or detract from the mix. The bottom line here is: the NIH conflict-of-interest regulations make it harder for NIH scientists to help private researchers. Now the FDA's new conflict-of-interest guidelines make it much less likely that able private-sector personnel can help the FDA discharge its obligations.

#### PART IV: CONFLICTS OF INTEREST IN UNIVERSITY-INDUSTRY COLLABORATIONS

Cooperation is as important in university research as it is in the government sector. One critical function of NIH regulation is to foster it. But here the problem plays out in a somewhat different fashion because the diffusion of influence and

excellence across institutions makes it more difficult for a single unsound policy to drive out all its rivals. Academic scientists address scientific problems until a “proof of principle” is established; then private firms take over the task of commercialization.

This division makes sense and has been a pillar of American science policy since the Bush Report of 1945. In basic research, scientists address general laws of nature that are not subject to the standard forms of intellectual-property protection and thus fit comfortably into the public domain, where state subsidy, not private reward, is the stimulus for production. But it is often the case that the individuals who developed the basic theory are in the best position to aid in its rapid and effective commercialization, which is why it is commonplace today for many basic scientists in universities to work on outside ventures of a commercial nature, in which they take an ownership or a patent position.

The logic for this dual existence makes economic and social sense. Universities are in the business of producing general knowledge that is fully accessible to all individuals at all times. Industry people are in the business of producing new commercial products that can be sold for a profit, precisely because they are of benefit to individuals, often very sick individuals, whom they are intended to treat. A person who knows something about a field of research can easily add value to a commercial enterprise when this knowledge cannot be obtained in any other fashion. To impose an absolute ban on these collaborations would be to force major scientists to take up residence in one camp or the other, in ways that could impoverish both. A total ban on these joint ventures would be most unwise and, for the most part, is not in place today.

Serious complications arise when research scientists assume dual roles in basic and applied research. The general ethic of basic science is full release of disinterested research into the public domain.<sup>26</sup> Openness and objectivity are its hallmarks. In contrast, the general ethic of commercial work is to keep all information secret until it makes sense to disclose it. The prospect of deals in which university scientists agree to accept industry norms is likely to raise hackles.

Thus Sheldon Krinsky, for one, refers back to an incident in which Betty Dong of the University of California, San Francisco, undertook work for a drug company to determine whether a generic drug was the bioequivalent of the original patented product. Once her research determined that it was the bioequivalent, the proprietary drug company exercised its right under contract to suppress the information, to the point of pulling the galleys for the study from *JAMA*.<sup>27</sup> Clearly, there is a gap in the system. It would be intolerable if any company were able to suppress negative findings about its own product in advance of its release.

Ordinarily, any contract between a proprietary company and a university is subject to FDA oversight, which would require submission of all negative data to that organization. The peculiar setting of bioequivalence, however, does not generate that kind of reporting obligation. The right policy—for this class of cases, at least—is to ensure that no university scientist undertake research that can be withheld from publication for competitive reasons, given the clear public relevance of the information to the general drug-approval process.

It is important to realize that the prohibitions against the publication of information that seem appropriate in this setting may not be appropriate in others. Many journals, including *The New England Journal of Medicine*, have general rules against the publication of articles by an author before they appear in the journal. The reason is that early publication undermines the subscription base of the journal—and ultimately, its ability to survive. Such rules come at the cost of early dissemination of information that could prove valuable in individual cases, but they exist for the sensible and simple reason that the long-term viability of the business depends on trade-secret protection.

I see nothing wrong with trade-secret agreements whereby university scientists agree that, as a term of their collaboration, they will not publish information that could damage or destroy the protection of intellectual property through trade secrets or patent. Indeed, the balance between openness and secrecy is a constant source of difficulty in university research. It is easy to think that all science should remain open,

but the dominant movement has been in the opposite direction. The Bayh-Dole Act of 1980<sup>28</sup> was passed to address the asserted problem that discoveries made in universities languished for lack of a commercial champion. The exact extent of this problem is hard to pin down, but the concern is easy to state. Once an invention or a discovery is in the public domain, no one will want to pursue its commercialization for fear that some unknown competitor will be first to market. Inventions supported with public dollars could thus face the problem that Bayh-Dole sought to address. The desire for coordination could thus lead all firms to forgo investment in a product that would have some punch if undertaken by any one of them.

This outcome seems at odds with general economic theory, which maintains that it is wise public policy to place already commercialized inventions in the public domain, where the expiration of patent protection makes the invention available to everyone free of charge. Yet the economics has not quite worked out the same way for particular inventions that it has for general scientific laws and substances. The key point seems to be that everyone is given a much clearer sense of the invention landscape by products that have been available on the market for many years while under patent protection.

But that level of knowledge is not available about new inventions that could be developed simultaneously by anyone and everyone. It seems that uncertainty over the commercialization of public domain products, which has to take place in secret, is so great that no company wants to develop a risky novel product application when other, more secure, options are available. In this context, one unanticipated benefit of patent protection is that it reduces the level of uncertainty and thus creates one willing and active market entrant instead of a dozen inert ones. The theory on this point is both complex and underdeveloped. But the empirical evidence of the rise of commercialization after Bayh-Dole is too great to ignore.

Even those who have doubts about its ultimate soundness recognize that Bayh-Dole has launched a veritable outpouring of university activities directed toward the commercialization of patented products

and technologies supported by federal monies. These activities, moreover, do not take place in haphazard fashion, for the law requires all universities to determine for themselves whether to patent a particular technology that their laboratories and scientists have produced with government grants. Making these assessments is no off-the-cuff matter, for all major research universities today have offices of technology transfer whose explicit mission is to examine these projects for their commercial potential. These technology transfer obligations are big business, and their character stamps modern science. Anyone who reads the scientists' manuals issued by major universities must be impressed by the importance and scale of the business, which tests traditional conceptions of scientific objectivity despite the university's official uneasiness over the place of the profit motive on its list of institutional priorities.

Bayh-Dole does not apply to projects that are not funded by federal money, but the model remains dominant in all research areas, including health care. Many universities, on their own initiative, have developed intellectual-property policies that impose explicit conditions on projects that are internally funded or otherwise undertaken by their own scientists and researchers. They include the statutes of the University of Chicago, which explicitly make all such inventions university property if done at the university or with its substantial assistance.<sup>29</sup>

The entire operation is big business, as the examination of the website of any office of technology management (OTM) reveals.<sup>30</sup> Biotech and pharmaceuticals are an essential part of this mix. The sums involved in these patents and projects run into the millions of dollars, and the preparation to exploit the gains from them is sophisticated and elaborate. Nothing happens at the university level if the university decides not to pursue an invention, at which point the inventor, subject to contractual limitations, is free to pursue it himself.<sup>31</sup> Yet if the university does get involved, it is obligated to give the inventor some share of the revenues, and it can call on the inventor to cooperate at the work's preliminary stages. "Companies know academic researchers will rapidly publish their inventions and the licensee values getting access to the invention

before its competition gets it from the literature."<sup>32</sup> These guidelines reflect full awareness that premature publication of various ideas contained in a patent can result in the loss of patent protection. The university therefore requests the early turnover of information to it for evaluation, which can precede publication. Publication may therefore be postponed to preserve patent protection.

Make no mistake about this transformation. Throughout this entire process, the OTM acts like other investors in trying to figure out what the investment is worth and in seeking out potential partners who can license the technology from the university for their own work. The usual practice is to defer the patent application until the licensing agreements are in place. It is not remotely conceivable that this effort could take place without the extensive cooperation of the original inventor in the internal process of the university, and there would seem to be no reason to preclude the participation of the inventor in the management of the project once the outside licenses have been completed, if that participation produces gains all around.

The watchword in these cases is "timing is everything" because the more lead time that the technology office has to evaluate the program, the more successful it will be. The bottom line is: "The technology transfer office is therefore like any other investor that seeks a return on its investment. Investing in a patent application that is not licensable is a bad business decision and costs the university money that could have been better spent on research and education."<sup>33</sup>

In the face of this entrenched practice are ethical concerns that these powerful economic forces will influence the choice of projects on which basic scientists choose to work.<sup>34</sup> The point cannot be denied. Yet it is difficult to know which way that inevitable proposition cuts. The first uncertainty is the difficulty of gauging the magnitude of the effect, given the other influences that any research scientist faces in the choice of research project. The need to gain NIH funding, to secure publication, to gain tenure, to collaborate with colleagues and superiors, and to establish a scientific reputation are themselves powerful forces that determine research behavior.

These factors could either work against the prospect of commercialization, or reinforce it.

The second response is simply: So what? Suppose that Bayh-Dole does direct research to commercial ends; why is that a bad thing? *Ceteris paribus*, a project that produces commercial gains benefits individuals, often desperately sick individuals, outside the academic community. Indirectly, it generates tax revenues for the government, some of which can be used to fund further research, and it offers proof that individuals outside the tight circle of academia have gained from the research, for they purchase only those products and services whose value to them exceeds their costs.

Any correlation between the soundness of the basic science and its commercialization is elusive at best. Any negative correlation between the two is doubtful, especially in light of the very low incidence of reported difficulties posed by practices that are deeply etched into the practice of modern research science. It is easy to think of some example of foundational research that has no direct commercial application. No one wants to block that research, whether funded by the NIH or any other source, public or private. Yet note that it is always even easier to conclude that that research is fundamental precisely because it generates a wealth of commercial opportunities: Was research on lasers not fundamental because it generated huge external benefits?

Showing these tangible benefits, moreover, could easily affect public support for basic research. Tangible inventions and therapies enable people to see what their tax dollars have bought. If we adopted that view, we would quickly dismiss the universal, if unsubstantiated, fear that the successful commercialization of basic research will sap the public's confidence in the entire academic enterprise.<sup>35</sup> Poor and abstruse research could have that effect, which is why congressional committees are always reading aloud the titles of projects funded not by the National Institutes of Health but by the National Endowment for the Arts or the Humanities. I am not aware of any public outcry over the commercialization of the basic research that led to the creation of the Salk and Sabin polio vaccines. To the contrary, public support for basic research increases when the public

sees tangible signs of improvement that follow directly from the research.

This urge for commercialization of basic research goes still further. Universities today are short on resources to conduct basic research. In many instances, therefore, they actively seek collaboration with pharmaceutical houses for the development of promising leads from basic science, which is why the University of California, San Francisco, has a separate Office of Industry Partnerships, which states that its mission is, as it should be, "Fostering Mutually Beneficial Partnerships," which could involve research collaboration, clinical trials, and technology licensing. Listed as the major asset of the university are its 15,000 faculty and staff and its 4,000 graduate students and 1,000 postdoctoral fellows. It should not be supposed that key personnel have nothing to do with the collaborations that follow. They clearly lie at the heart of a business that takes the Bayh-Dole model and extends it to all sorts of joint projects.

The logic here is painfully simple. Once it is seen that the model of collaboration works for research covered by Bayh-Dole and for internally generated research, why not apply the same principles to research funded by outside sources? The new collaborations provide additional funds for work inside the university and also provide jobs for recent graduates of the doctoral programs who might otherwise have to leave scientific work altogether. Whether or not Bayh-Dole applies, there remains, of course, an imperative need to ensure, save in rare circumstances, that Ph.D. supervisors do not press their graduate students into dual service. There is just too much of a risk that setbacks in one area would influence the evaluation of their degree work. And it is probably wise to prohibit the direct hiring of graduate students into commercial operations run by their advisors, at least for several years.

Even here, a note of caution has to be introduced, because however many basic scientists do basic biological research, the extreme specialization in these occult fields endows certain researchers with rare skills. At that point, it may be sensible to have an oversight committee pass on the possible appointment, attaching what conditions may be suitable in order to avoid

serious conflicts of interest. It is one of these difficult areas in which hard-and-fast rules tend not to work well. Some level of sound discretion is needed, for both extremes are untenable. Blocking these arrangements is deadly to scientific advancement; allowing them all to go unsupervised invites serious ethical lapses. The middle course wins, by default, and so the secret to successful administration is to ensure that the conflict-of-interest tail does not wag the entrepreneurial dog. To do so requires paying great attention to potential conflicts, for even a single failure in, say, a clinical trial could have repercussions large enough to place major programs in serious jeopardy.

The most vivid example of this problem involved the death of eighteen-year-old Jesse Gelsinger during his participation in a human gene therapy program, in which the director of the University of Pennsylvania Gene Therapy Institute and the university itself had financial interests in a company that stood to profit if the therapy proved successful.<sup>36</sup>

Yet any individual who is a potential participant in these programs has a keen interest in the other safeguards built in to their operation. In this instance, these were extensive.<sup>37</sup> In addition, they might well regard the financial stake of the investigator as a positive on the simple ground that no one is likely to invest time and money in a venture that is likely to fail. It is therefore doubtful that Gelsinger or his parents would have refused treatment for what was, after all, a degenerative condition for which no viable alternative treatment was available. Nor is it certain that the actual physical cause of death was related to the treatment. Gelsinger's was the first reported death from gene therapy, and no others have been reported since. The inevitable wrongful-death action that followed resulted in the Gelsingers' receiving an undisclosed settlement in what looks like a doubtful case. But the true loss from the entire incident was a combination of bad publicity and increased regulatory oversight on the standard principle that visible losses always prompt a powerful government reaction at the same time that the losses from forgone treatments are hidden and thus ignored.

The real risk in these cases is the regulatory overkill that can easily follow from a single debatably adverse

event. The central question is whether to include additional remedies beyond disclosure, including the strict separation of drug inventors from clinical trials, as the Institute of Medicine has recommended.<sup>38</sup> Here again, the per se rule seems advisable when someone else equally competent is able to supervise the treatments. But these markets are often quite thin, and I am leery of sacrificing expertise for the sake of dealing with the conflict of interest. A better policy might be to establish an oversight committee or to have a co-principal investigator deal with the conflict. After all, it is highly likely that any other distinguished researcher in the same field will have a different conflict of interest, such as an interest in some rival technology. The management of research, as of everything else, requires such exercises of intelligent discretion.

The constant effort to control against conflicts of interest is manifestly reflected in the decision of Partners HealthCare, which owns the Massachusetts General Hospital and Brigham and Women's Hospital in Boston, to impose a strict limitation of \$5,000 per day that its senior officials can receive in compensation for sitting on the boards of pharmaceutical and biotech companies.<sup>39</sup> No legal or regulatory barrier prohibits Partners HealthCare from imposing this restriction on its employees, at least if we put aside the (weak) possibility that these new restrictions will be in breach of its individual contracts.

The question here is one of institutional prudence, not legal compulsion. On that level, the guidelines fare badly. To be sure, the opening sally of Partners HealthCare is that industry interactions are "fundamental to the mission of Partners and other academic medical centers."<sup>40</sup>

But that is mere lip service to an ideal in a report that contains not a single recommendation for expanding or deepening the connections between the two groups. On the financial issue, the initial impulse is to limit academic faculty members to consulting levels that are thought to be "befitting" their rank and position, which cashes out at \$500 per hour, well below market levels for these experts. In so doing, this approach differs sharply from the "conflict of commitment" limitations (no more than 20 percent of one's time spent on outside work, or up to one day per week)<sup>41</sup> that Partners HealthCare

requires of its physicians, on the simple ground that individuals should not be paid by one organization when they are, in fact, working for another. The exact amount of time permissible for outside work, of which consulting is only one component, is a matter of business judgment, which would be hard to fault for imposing any institutional restrictions.

The interaction between the two sets of restrictions requires attention. One way to retain skilled individuals at Partners HealthCare and anywhere else is to allow them to sell their services to the highest bidder, so long as conflict-of-interest guidelines are met. A greater ability to command higher incomes should reduce the base salaries that Partners HealthCare and others have to pay to attract and retain the physicians they need. The organization can then use the released funds to further other essential activities of the business. In addition, extensive connections with outside organizations offer the clear advantage of educating participating doctors and senior officials on matters outside their home organization, which, in turn, could improve their performance of their basic job.

What is striking about the Partners HealthCare program is that it does not identify actual abuses for which the salary cap on outside work would be an effective remedy. In the short run, it is unlikely that these restrictions will produce an exodus from the business. Relocation costs are expensive, and the other beneficial features of the job could weigh heavily in the calculus of individuals deciding whether to stay at Partners.

It is thus instructive that the one named official was Dennis Ausiello, who serves both as chief of medicine at Massachusetts General and as chief scientific officer at Partners. He earned a reported \$220,000 per year consulting with Pfizer.<sup>42</sup> Would we prefer a world in which he spent twice as much time on the outside to earn the same amount of money? Or one in which he eventually leaves the institution to work elsewhere? Over the long run, these restrictions should curtail both retention and new hiring, especially if the gap between regulated and market rate remains substantial.

Those points did not seem to matter to the eminent committee at Partners HealthCare, which offered no

systematic analysis of the incentive effects of its new regime on all key actors within the system. It is a case of myopia born of overconfidence. Perhaps it will work at Harvard, but I doubt it. It will be difficult to replicate at many other institutions, which are likely to see this as a competitive opening to woo people away. If, by some chance, Partners HealthCare starts a trend, the long-term prediction is that the constriction of opportunities will decrease the share of researchers going into academic research by some appreciable degree.

In sum, outside the booming area of technology transfer, the grim pattern of overkill continues to cut down opportunities for industry scientists, on the one hand, and universities and government scientists, on the other. These restrictions could be justified if there were some evidence of a deeply ingrained set of abuses. But we are not dealing with some untried enterprise where we can only speculate about the extent of abuse, and might therefore be unwilling to embark on a course of action that could prove harmful in the long run. Rather, we have had the benefit of these collaborations ever since the publication of the Bush Report in 1945 without having seen any sign of the systematic abuse that could justify the tough bans that have been put into place.

At this point, the dangers of overkill seem apparent. They are driven, I fear, by a populist impulse that finds it unnerving that academic excellence should yield a generous financial return. This impulse, as will quickly become evident, arises in response not only to the way in which pharmaceutical firms seek to develop new products; it arises with equal, if not greater, fervor in response to the way in which these products are marketed.

## PART V: CONFLICT-OF-INTEREST REGULATIONS IN DRUG AND DEVICE MARKETING

**T**ough new restrictions on conflicts of interest are also the order of the day in the marketing of drugs and medical devices. In April 2010, the Council of Medical Specialty Societies (CMSS) imposed tough

new regulations on conflicts of interest. The council's involvement is no small matter, for it represents thirty-two medical societies comprising about 650,000 members.<sup>43</sup>

This umbrella organization includes the American College of Physicians, representing specialists in internal medicine; the American College of Cardiology; and the American Society of Clinical Oncology—all of which are major practice areas. Once again, the dominant trope is that of total separation, which includes an injunction that the heads of member medical societies and the editors of major medical journals sever all financial and consulting arrangements with the pharmaceutical and medical-device industries.

One peculiar omission from this work appears to be connected to medical studies done with an eye toward litigation. Thus, in a detailed exposé of the matter, Dr. Laurence Hirsch, a former Merck employee, has documented several instances in which it appears that medical researchers have published academic articles on matters in which they were expert witnesses in litigation without disclosing the extent of their involvement.<sup>44</sup> Thus, in one article critical of Merck's role in promoting Vioxx,<sup>45</sup> the authors' disclosure statement to the AMA said, "All of the authors have been compensated for their work as consultants at the request of plaintiffs in litigation against Merck & Co, Inc. related to rofecoxib [Vioxx]." Yet it did not list the amounts of money received for doing work in these cases, which turned out, in one case, to exceed \$300,000, and in a second to be between \$2 million and \$2.5 million for testimony on Vioxx matters.<sup>46</sup>

It is worth noting that the *JAMA* editors have been among the most insistent on a wall of separation between industry and medicine.<sup>47</sup> This episode is not the only instance of some highly controversial activity by a major medical journal in connection with litigation. A similar incident involving the Vioxx litigation arose with *The New England Journal of Medicine*. The evening before *NEJM* personnel were scheduled to have their own depositions taken in the Vioxx litigation, its editors, on the advice of their public relations consultant, leveled charges of academic fraud (technically called a statement of concern) against both Merck and independent scientists for their research on Vioxx.<sup>48</sup>

*NEJM* claimed that these scientists had all manipulated data in an effort to minimize the importance of research that showed elevated cardiovascular risk in patients taking Vioxx, but the charge hinged largely on the assumption that the Merck study had adopted an improper protocol for choosing termination dates and had chosen different ones for the gastrointestinal and cardiac arms of the test. In fact, the independent design committee in charge of the study had made the decision to choose dual end points long before the results were known. The earlier date for ending the cardiac arm of the trial had an innocent explanation—the desire to speed the entire study to publication, given the greater length of time that the cardiac results took to analyze than the gastrointestinal ones. In any event, the overall results would not have changed much, even if identical end points had been selected for both arms of the study. The *NEJM* editorial's criticisms did not comply with procedures for dealing with charges of scientific fraud adopted by the International Committee of Medical Journal Editors, to which *NEJM* subscribed. These require examination of the charges by the authors' sponsoring institution. Not surprisingly, there is no report that any home institution investigated its own scientists for academic fraud.

The conflicts of interest show that the ancient question "Who guards the guardians?" has yet to receive a definitive answer. Apparently, it has not dawned on journal editors, who continue to inveigh against industry influence in categorical terms, that even they are not beyond reproach.

Thus CMSS's first principle of interaction reads, categorically: "1. *Independence 1.1*. Societies will develop all educational activities, scientific programs, products, services and advocacy positions independent of Company influence, and will develop and adopt policies and procedures that foster independence." The remainder of the guidelines dealing with corporate sponsorships<sup>49</sup> or with society meetings<sup>50</sup> take the same hard-line attitude.

Once again, the policies are clear enough, but are they wise? Research and development involve the creation of new products. That endeavor, however successful, will produce enduring social gains only if the producers of pharmaceutical products and medical devices can sell

these products in the broader market. The economics of this enterprise are daunting. It takes a dozen or more years to bring a new molecular entity to market. Most efforts to put drugs through the clinical process end in failure, as a growing fraction of promising products is unable to run the ever more exacting gauntlet that is set by both patent and FDA policy.

It follows that strict conflict-of-interest regulations on promotion and marketing will increase the cost of getting a new drug to market and thus delay its effective use. The increased costs, moreover, have to be recovered over a relatively short period of time, typically nine to eleven years, and never longer than fourteen years. The only way to reach this goal is to aggressively market information to the trade (physicians, clinics, and hospitals) and, in some instances, to the public at large. These marketing activities are especially critical because of the cost structure for the production of new drugs. The first pill costs over a billion dollars to make. The subsequent pills often cost pennies or dollars. The system works only if the pharmaceutical company can backload some of the initial costs of production onto the subsequent rounds of drug sales.<sup>51</sup> At that point, the expenditures on promotion and advertisement yield a high rate of return because they allow the cost of that initial pill to be divided over all subsequent units. A company that is not able to market the drugs cannot, quite simply, afford to make them.<sup>52</sup>

It is easy to dismiss a plea of this sort if one thinks of all these new drugs as non-improvements in the first place. Why spend for new advertisements if a handy generic can do the job? No one doubts that the increased share of generics in the marketplace is one of the profound transformations of the last generation. But it hardly follows that there is always a generic substitute for a new molecular entity. Instead of prejudging any head-to-head comparison of old and new drugs, the point is to ensure that the manufacturers of both types of drugs are able to put their best foot forward, which they cannot do if there are ample inhibitions on permissible marketing practices.

So the question is then asked: Just what does marketing do? One obvious function is simply to ensure that

people in the profession are aware that a new drug has made its way through to the marketplace. At this point, many devices enable prospective users to evaluate the drug without having to rely exclusively on what drug companies say, directly or indirectly, about their products. The *Physicians' Desk Reference* contains a wealth of relevant information, and many intermediate organizations, such as the National Comprehensive Cancer Network,<sup>53</sup> do their own evaluation of new and existing products, to which physicians and hospitals can gain access.

These entities are sophisticated parties that can, and do, form committees to make key procurement decisions that involve explicit head-to-head comparison of two or more drugs on price, effectiveness, safety, and convenience. No one could think that regulation of how pharmaceutical companies promote their drugs was a useful counterweight to some monopoly position of the drug manufacturer. The patent gives an exclusive right to market only a particular drug. It does not preclude the marketing of close substitutes with which comparisons are appropriate.

It is important to note that the availability of some public sources of information does not eliminate the need for others. New drugs are complex chemical products that require a close understanding. Sending out representatives from the company or from medical practice to explain what their complications might be, and how they should be addressed, is one way to get additional information quickly to doctors who may want to prescribe these drugs and to institutions that must decide whether to include these drugs in their standard formulary, which would allow them to be routinely prescribed. It seems sensible to let companies pay physicians to do this kind of work. It is not as though they are free to engage in mass fraud. Any claims that these doctors make will be attributed to the company that hired them, and if those claims go beyond those approved under the FDA, the company could easily suffer substantial exposure to tort liability or regulatory sanctions.

In addition, there are always practice tips from parties who have had experience in prescribing a drug. These tips are given out not to naïve audiences

but to physicians who face their own reputational and liability risks when they prescribe drugs. In most of these sessions, physician questioning plays a prominent role, and there is little reason to think that companies will push risk-making claims that could lead to improper uses giving rise to serious tort liability, including awards of punitive damages, in multiple cases. All their statements are made in public settings, which makes it difficult to spread systematic falsehoods. The information market is itself live with active competition. Powerful institutional forces, from insurance companies to pharmacy benefit managers, often urge the use of generic drugs in head-to-head competition with their more expensive branded rivals. These forces offer at least some counterweight to the implicit tax and insurance subsidies for new drugs.

Rival companies are free to promote their own branded drugs, all with the same set of business and tax incentives. Likewise, proponents of generic drugs are always free to make their case as well. Even if we assumed that there was some degree of bias in an individual presentation, that bias in the one case is likely to be countered by other presenters, who are free to pounce on any errors or excessive claiming. The existence of some kind of a skew in the presentation of data does not count as a decisive reason to close down or limit the operation of this market. Moreover, a larger number of entrants helps shorten the cycle between the presentation and correction of a false claim.

All this presupposes that these biases enter in a systematic way. Many studies claim that this is the case and that these biases typically enter through the articles of authors who often become paid lecturers to promote the research contained in their published papers. The overwhelming weight of this evidence is that authors who have a financial connection with a particular company provide evaluations that are, on balance, more favorable to the companies for which they work than do independent investigators who write on the same topics.<sup>54</sup> But what inferences should be drawn from this common result?

The first question is: Which investigators have the bias? That question is not as idle as it sounds, if the negative studies are conducted by physicians whose

devotion to generic drugs creates a built-in hostility to new, branded drugs. The refusal to take payments does not eliminate ideological preconceptions that could bias evaluation. Ironically, there are no institutional safeguards against physicians whose denunciations of branded drugs are over the top. Put otherwise, nonpaid physicians in comparative drug trials do not necessarily form an ideal control group. An independent study needs to validate their judgments, which is hard to do experimentally.

Even if there were some bias in individual studies, it is far from clear that these biases cumulate, given the presence of powerful market pressures that tend to cancel them out. Thus, if each of two companies with competing products overclaims relative to the other, a reader of both studies cannot be misled by both studies simultaneously. The question is only the relative influence of the two studies, which is difficult to measure in the abstract and even more difficult to measure when independent evidence from other sources, including the champions of generic products, is put into the mix.

The same strong pressures for the use of generic medicines offer a counterweight to the selling points of the products of both companies. It is not credible to think that within this dense institutional framework, the risk of bias swamps the transfer of information. Nor is it credible to think, as has often been suggested, that these small gifts create an implicit obligation on the part of physicians to reciprocate by purchasing large quantities of the drug.<sup>55</sup>

First, it seems unlikely that the gift of a fountain pen will call forth the purchase of large quantities of drugs for a long period of time. Second, in most institutional contexts, no single individual has control over these decisions. Simple disclosure of the gift to the group could therefore effectively smoke out this bias. Third, this form of reciprocation cannot effectively be carried out in any case where two or more organizations supply the same type of gifts for private gain. Just whom do you favor and why, after hearing five separate presentations? Fourth, condemnation of industry authors presupposes that their purported bias does not reflect their true beliefs. But the innocent

explanation may stem from a genuine selection effect, whereby physicians promote or purchase only those drugs in which they already believe. Fifth, the social-welfare consequences of these errors are hard to identify.

The usual claim at the end of these studies is not that there is some systematic error whereby inferior products are able to displace better ones. As noted earlier, there is only the far weaker claim that these widespread conflicts of interest can “influence biomedical research in important ways,”<sup>56</sup> which, as Paul Rubin has pointed out, is far from saying that the conflicts have led to changes in medical practices that have raised costs or harmed patients.<sup>57</sup> To conclude that the weaker claim has validity requires an examination of not only the content of the various studies but also their influence on physicians as a group, which is exceedingly difficult to do because doctors or experts in one field rarely look at one study in isolation but instead look at studies in connection with one another and other materials.

In principle, then, there is no reason to suspect an epidemic of bad faith among the pharmaceutical firms in the delivery of information to the medical profession, whether through staff or independent physicians. Strong critics of the current practices generally offer no empirical evidence of the extent of any supposedly malign influence. Their work is largely a priori and, as such, has not closely examined the patterns of dissemination of medical information from the pharmaceutical industry through customary channels, with their present set of institutional safeguards. Instead, these critics ask the proponents of drug promotion to meet an impossible standard of proof when they insist that the medical profession cannot function well unless “the public and the profession can be certain that a PMA [Professional Medical Association] dependent on industry for support is being faithful to its mission of conducting education programs and setting practice guidelines that reflect only the best scientific knowledge.”<sup>58</sup>

But certainty is a very high standard to set in an area as fraught with difficulties as this one is. To so insist is to assume that one kind of error—reliance

on bad information—dominates all other errors, including the systematic reduction in the amount of available information when these industry sources are closed off. Many a hypersensitive ethicist thinks this way, but there is no evidence that the public at large, or even the ordinary physician, embraces this one-sided approach.

It would be useful to have direct evidence of present major physician or public dissatisfaction with the role that drug companies play in the dissemination of medical knowledge. Sparse as reliable information is, one recent study suggests that the fear of contamination and corruption is overblown, at least in the professional education of physicians. A review of continuing medical education (CME) at the Cleveland Clinic polled more than 95,000 practitioners, who were asked to evaluate the benefits that they received from various lectures—some given with, and some without, financial support from the pharmaceutical industry. An overwhelming number of participants thought that the presentations they attended were free of bias, regardless of whether the speaker had received commercial support.<sup>59</sup>

When 97.3 to 99.2 percent of the participants report that their experiences with both kinds of lectures is about the same and has been excellent or good, a celebration, not a crackdown, is in order. There is certainly no evidence of the superiority of one kind of presentation over the other, and no a priori reason to think that the sharp truncation of medical evidence in the name of neutrality would improve the overall level of physician performance. A lot of flawed information may be better than no information at all, especially when members of the profession have limited even individual and institutional means for self-correction.

Notwithstanding the flaws or shortcomings inherent in any single source of information, in aggregate the market is undoubtedly improved by competition. Nonetheless, many leading medical authorities insist on making the best the enemy of the good. There are thus many unequivocal recommendations from high places to eliminate any role for pharmaceutical companies in the conduct of medical education. In a major 2009 *JAMA* article, David Rothman<sup>60</sup> and ten

distinguished colleagues put their perceptions of mission integrity above all other considerations and urged dramatic solutions, many of which have been implemented—for example, the conflict-of-interest regulations adopted by Partners HealthCare.<sup>61</sup> All these recommendations suffer from the common failing of overstating the benefits and underestimating the costs of their desired program.

The first recommendation of Rothman et al. is to eliminate all funding of Professional Medical Association educational activities if possible, except for booths at which companies can advertise their products. The grim reality is that a large portion of these budgets is now paid by pharmaceutical companies, and at a time when hospitals and clinics are hard-pressed for revenues, no alternative source of funding is evident. The authors recognize this impasse and hope to cut down the pharmaceutical component to 25 percent of the total bill in the short run. But they are equally uninformative as to how to fund the other 75 percent of activities. In general, it seems far wiser to allow many voices to speak than to have none speak at all. Overestimate the estimate of bias in the presentation of information, and nothing is taught. The proposal is far too stringent.

One further consequence of this systematic hostility to pharmaceutical funding stems from employers' denying their own physicians the right to receive compensation from drug companies to speak at these events, which is, in fact, one part of the overall 2009 Partners HealthCare proposal. But if it makes no sense for the PMAs to keep paid physicians off their programs, it makes no sense to treat doctors as though they have neither intelligence nor morals by imposing a per se ban on their participation.

The demeaning nature of this ban has not escaped the attention of physicians who are covered by it. At least one physician, Paul M. Copeland, did express frustration with the ban, which kept him from signing up for about a dozen appearances per year, for sums of \$1,250 to \$2,000 (which might not even have compensated for the loss of time seeing patients or spent in the lab), at which he speaks about the various drugs and fields questions for about an hour after

he speaks.<sup>62</sup> Copeland's conclusion was that patients and doctors both benefit from these activities, which is why the ban is so "disheartening." It is not easy to determine how widespread this sentiment is. But it is worth noting that Copeland is an assistant professor. The issue of morale hardly cuts in one direction, as Rothman and his colleagues maintain.

Once the drug companies are effectively prevented from hiring individual speakers, what might be done? One possible strategy would be for companies to contribute money to a program that deals with the drugs and diseases in which the company has an interest. Just discussing the problem could be of benefit to the drug company, even if it cannot select the messenger. Indeed, even without the ban, companies might want to make a supplemental contribution of this sort.

But in the brave new world, the ethicists are intent on seeing that this evasion does not get off the ground. Instead, Rothman and his coauthors insist that any such contributions be made to a "central repository," so as to ensure that drug companies have no influence over choice of topic or personnel. They make the same proposal with respect to the funding of CME and for any research projects that an industry group might want to fund in its area of specialization. They also think it profoundly unwise to allow industry representatives any role in the selection of speakers for any of these programs.

In all cases, the correct response should take the same tack. Why should any organization devise treatments for which there is no return benefit? The sustainability of commerce depends on expenditures that work for mutual benefit. Yet these expenditures will not be made if the organizers of PMA events continue to think in zero-sum terms: if the company benefits, the profession must lose. Yet it is just this deeply suspicious attitude that will lead companies—quite rightly, in my view—to refuse to play ball with PMAs that think that drug companies should just open the financial spigots. The proposed policy is born of distrust, which, when communicated, can only increase the estrangement between industry and the medical profession.

The same theme of hostility applies to the critics' view of the proper degree of participation of industry experts in setting clinical standards, practice guides, or outcome standards—total separation. That position seems particularly perverse because of the enormous stake that these companies have in participating in the setting of standards by which their own clinical trials will be judged. The removal of academics who work with industry from these various selection committees could easily prove to be a serious negative. They have information that is not available to other members of these committees. Their interests are certainly not in conflict with every proposal. To articulate the wrong outcome standard or end point in a clinical trial could waste hundreds of millions of dollars. No one has ever suggested that industry dominate the committees on which individual members may be invited to serve. But surely, standard practice, which allows industry's input and participation when subject to medical oversight, makes sense. These committees that set standards for clinical studies can work only if they receive funding from pharmaceutical companies, which cannot be expected to foot the bill if they are to be systematically excluded from the standard-setting process. Of course, the input of independent physicians is critical. Yet by the same token, that participation will be more measured and informed if these committee members are joined by industry representatives.

It is commonly said about the medical profession that the demands of industry are so great that all competent physicians are enlisted to work at some time with one or another company. If we impose the ban under discussion, the only persons left to make the decisions will be those whose credentials and expertise are not up to the difficult challenges in these areas, or those who have such deep hostility toward the industry that their functional neutrality is rightly called into question. Yet of these risks, there is not a word in the recommendations that Rothman and his coauthors make. The systematic implementation of their proposals is likely to make a shambles of all forms of continuing medical education.

This attitude of strict separation has, for the most part, been implemented by private associations. It may not, however, be a coincidence that the one major

legislative initiative to deal with the supposed abuses characterizing relations between drug and device companies and physicians illustrates the pitfalls of the voluntary strategies that gravitate toward complete separation. I refer here to the so-called Pharmaceutical and Medical Device Manufacturer Conduct Act,<sup>63</sup> which is now in effect in Massachusetts. The provisions of this statute are difficult to summarize, given the usual thicket of technical definitions and muddied prohibitions. The statute creates a “marketing code of conduct” of great rigidity and specificity. The multiple provisions of that code are intended to ensure that pharmaceutical and medical-device companies are debarred from using any kind of gift, be it in cash or in kind, to persuade key medical and health-care personnel to acquire their goods and services. The restrictions are quite onerous. The statute starts from the same dubious premise that there has been a breakdown in the manner in which medical products are ordered, and thus it seeks to impose a code of fair conduct that is at wide variation from customary practices within the field.

One recent story gives an account of the difficulties that arise in this area.<sup>64</sup> In order to make presentations about products for sale, it is necessary to find a large forum to make a medical presentation. It is also necessary to make it profitable for valuable professionals to spend time at these sessions. The legislation unfortunately looks askance at any meeting that is provided outside of hospital premises, of which there are many. How else is one to read a prohibition that says that the marketing code “shall not allow (1) the provision of or payment for meals for health care practitioners that: . . . (c) are offered, consumed, or provided outside of the health care practitioner's office or hospital setting”?

Joint presentation by multiple vendors was simply not contemplated under the law. That is just one symptom of a larger problem: the promulgation of rules and regulations without any real inquiry into how the procurement of complex equipment works. As usual, trade publications give the pulse of the act, and these note how difficult it is for companies to comply with a law that carries with it a fine of \$5,000 for each violation—which can easily mount up if

each “transaction, occurrence, or event” is defined as a separate violation. Unfortunately, the scope of a violation is left unclarified in the statute and the regulations. Nothing in this language indicates whether running two promotional sessions at two locations for 1,000 people counts as one violation, two violations, or 2,000 violations. The *in terrorem* effect of such a law should be evident.

What makes matters worse is that the proposed rules cut so deeply into customary ways of doing business, despite the absence of evidence of systematic abuse. In most instances, the proper response is simply to avoid conducting activities inside the state, for fear of cumulative penalties. One consequence: Boston cardiologists no longer receive the benefit of training sessions funded by medical-device companies, plural. Their pooling activities are a useful safeguard against bias. But under the statute, they are all exposed to sanctions for cooperative activities, whose ramifications are not spelled out in the statute or the regulations. Even such routine matters as training in the use of medical devices can offer a challenge. One sensible technique is to give preliminary instruction in the use of medical devices before purchase. Yet this is regarded as impermissible under the act, on the ground that a corned-beef sandwich could drive a purchase decision.

Yet no one knows what to do when the physicians who need training on the devices prior to a purchase decision do not have the power to make the purchases in question. Such “soft contracts” may comply with the law—but then again, they may not. The safe harbor is to refuse to give instruction within the state, which is to the benefit of no one. Overkill and disproportionality have spread from the institutional to the legal arena.

## CONCLUSION

The innovation and commercialization of new drugs and new medical devices is one of the central missions of our entire biomedical complex. In working through these arrangements, the sensible distribution of responsibility is heavily weighted toward public efforts to underwrite the

development of basic science, up to the point of proof of principle. Broad scientific laws rightly receive no protection under either the patent or the copyright system. It is therefore sensible to rely on public support for what is, after all, the creation of public goods.

In science, as in other human endeavors, one difficult question involves the transfer of information across institutional boundaries. These efforts are necessarily imperfect, for no set of institutional arrangements can guard simultaneously against all forms of error. It is dangerous in the extreme to pose the question as though the only task in question is to rid the medical profession of conflicts of interest in the service of some laudable, if abstract, ethical ideal. It is often well advised to accept these conflicts of interest as a necessary part of doing business and manage to the point that the last dollar spent in seeking to prevent error generates the same return as the last dollar spent on any other phase of medical research. That program therefore looks to an interior solution, where disclosure of applicable conflicts opens the way for their intelligent management. Trade-offs, not moral absolutes, should dominate this approach.

In looking over the huge expanse of scientific inquiry, one should not take the occasional shipwreck as a sign that the system is irreparably broken. Rather, it should be taken as a testimony to the strength of a traditional set of ethical norms and institutional safeguards. As the stakes of various activities become higher, the need for collaboration will necessarily increase and so, too, its risks.

It is perfectly appropriate to devote more resources to the monitoring of conflicts of interest. But a few incidents of misbehavior should not lead to a total reorientation in attitude such as that championed by the “ethical” portion of the medical profession, which does not trouble itself to inquire into the costs and benefits of collaboration in connection with the innovation and dissemination of new and valuable therapies. The errors committed on its account are not small, and any systematic implementation of this program is likely to retard, not advance, medical progress. In some instances, we can attribute the difficulties to legislation, such as the ill-fated Massachusetts law. But

in most cases, a peculiar mix of ethical absolutism and political populism drives the medical elites toward the wrong policies.

It is with great frustration that I have offered this detailed critique of many of the conflict-of-interest policies of the NIH, the FDA, and private universities. The issue is purely one of judgment; it is not about their legal right to run their businesses as they see fit. Yet it is a serious business when the medical elites have so misperceived the costs and benefits of their dogmatic approach that they are likely to harm the

very patients whom they seek to help. It is easy for people to believe in the invocation of some form of a “precautionary principle,” in which the objective is “better safe than sorry.” But, as noted earlier, there is no safe harbor in designing institutional arrangements for dealing with high-risk decisions. The effort to be safe could easily leave you sorry. In this instance, the policies of government agencies and private institutions concerning risk have gone way off to one side. The response is wildly disproportionate to the supposed severity of the turn. Let us hope that the powers that be in these areas wise up before it is too late.

## ENDNOTES

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1. For my view, see Richard A. Epstein, *Simple Rules for a Complex World* (Cambridge, Mass.: Harvard University Press, 1995).
2. Tomas J. Philipson and Eric Sun, "Cost of Caution: The Impact on Patients of Delayed Drug Approvals," Manhattan Institute, Project FDA Report No. 2 (June 2010).
3. Harvard University, "HMS Faculty Policy on Conflicts of Interest and Commitment," <http://hms.harvard.edu/public/coi/policy/coipolicy.html>. Note that a conflict of commitment deals with the amount of time that a member of an academic faculty can commit to outside business activities and still remain in good standing at his or her home institution. I do not speak about these commitments here.
4. See, e.g., charitable conflict-of-interest form, <http://www.ag.state.mn.us/pdf/charities/ConflictInterestPolicy.pdf>; and 3M Business Conduct Policies, [http://solutions.3m.com/wps/portal/3M/en\\_US/businessconduct/bcmain/policy/policies/protect3m/conflictinterest](http://solutions.3m.com/wps/portal/3M/en_US/businessconduct/bcmain/policy/policies/protect3m/conflictinterest).
5. For what is still the most dramatic incident of that result, see Morton Hunt, "A Fraud That Shook the World of Science," *New York Times Magazine*, November 1, 1981, <http://www.nytimes.com/1981/11/01/magazine/a-fraud-that-shook-the-world-of-science.html?&pagewanted=print>. For my recent evaluation of this and other overt frauds, see Richard A. Epstein, "Academic Fraud Today: Of Social Causes and Institutional Responses," *Stanford Law & Policy Review* 21 (2010): 135. The peculiar dynamics of this fraud reached into the medical schools at Yale and Johns Hopkins, and the ramifications of this incident extended to both Columbia and Harvard. Columbia retracted its offer of a chair to Dr. Philip Felig, whose lax oversight failed to detect the fraud. The fraud was detected by Dr. Jeffrey Flier, now dean of Harvard Medical School.
6. For more information, see note 25 below.
7. For further discussion, see n. 26 below.
8. For my earlier account of the event, see Richard A. Epstein, "Mad Scientists: Go Away, Ethics Police. Leave the NIH Alone," February 15, 2005, <http://www.slate.com/id/2113520>.
9. The scientist involved, Dr. Trey Sunderland, was subjected to criminal charges toward the end of 2006; see "NIMH Scientist, Trey Sunderland, Charged with Felony Conflict of Interest \$\$ Pfizer," December 4, 2006, <http://www.ahrp.org/cms/content/view/405/119>. See also David Willman, "NIH Scientist Charged with Conflict," *Los Angeles Times*, December 5, 2006, A11. Sunderland pleaded guilty to a misdemeanor charge in December 2006. Pfizer was never charged with any wrongdoing, nor was any evidence advanced that it had not complied with its duties. See "Sunderland Pleads Guilty to Criminal Conflict of Interest," Health Care Renewal, <http://hcrenewal.blogspot.com/2006/12/sunderland-pleads-guilty-to-criminal.html>, December 11, 2006.
10. The comment was in the relevant blog entry, <http://hcrenewal.blogspot.com/2006/12/sunderland-pleads-guilty-to-criminal.html>. I agree with Anonymous, too. I understand that the tissue samples were intended to help develop a new diagnostic for Alzheimer's disease. Pfizer does not sell any diagnostics, so it would have generated no direct

revenues if this had been successful. The nature of the work was something that the NIH would have been proud of—and it got a bargain by having someone else pay for the work. The crime was nondisclosure and failure of form filing. The ethics of the project itself were superb.

11. The relevant numbers are not hard to find: the NIH invests over \$30.5 billion annually in medical research for the American people, <http://www.nih.gov/about/budget.htm#note>. More than 80 percent of the NIH's funding is awarded through almost 50,000 competitive grants to more than 325,000 researchers at more than 3,000 universities, medical schools, and other research institutions in every state and around the world. About 10 percent of the NIH's budget supports projects conducted by nearly 6,000 scientists in its own laboratories. National Institutes of Health, Research for the People, <http://www.nih.gov/about/budget.htm>.
12. Quotations that follow are taken from NIH, "Summary of NIH-Specific Amendments to Conflict of Interest Ethics Regulations," [http://www.nih.gov/about/ethics/summary\\_amendments\\_08252005.htm](http://www.nih.gov/about/ethics/summary_amendments_08252005.htm). For these purposes, none of the details matters.
13. National Institutes of Health, Office of Technology Transfer, Licensing Policy, [http://ott.od.nih.gov/policy/phslic\\_policy.html](http://ott.od.nih.gov/policy/phslic_policy.html).
14. Government should provide suitable incentives to industry to conduct research "by strengthening the patent system so as to eliminate uncertainties which now bear heavily on small industries and so as to prevent abuses which reflect discredit upon a basically sound system." "Science The Endless Frontier," A Report to the President by Vannevar Bush, Director of the Office of Scientific Research and Development, July 1945, <http://www.nsf.gov/od/lpa/nsf50/vbush1945.htm>.
15. *Ibid.*, V: Patent Policy: "The public interest will normally be adequately protected if the Government receives a royalty-free license for governmental purposes under any patents resulting from work financed by the Foundation. There should be no obligation on the research institution to patent discoveries made as a result of support from the Foundation. There should certainly not be any absolute requirement that all rights in such discoveries be assigned to the Government, but it should be left to the discretion of the director and the interested Division whether in special cases the public interest requires such an assignment. Legislation on this point should leave to the Members of the Foundation discretion as to its patent policy in order that patent arrangements may be adjusted as circumstances and the public interest require."
16. See *ibid.*: "The most important ways in which the Government can promote industrial research are to increase the flow of new scientific knowledge through support of basic research, and to aid in the development of scientific talent. In addition, the Government should provide suitable incentives to industry to conduct research, (a) by clarification of present uncertainties in the Internal Revenue Code in regard to the deductibility of research and development expenditures as current charges against net income, and (b) by strengthening the patent system so as to eliminate uncertainties which now bear heavily on small industries and so as to prevent abuses which reflect discredit upon a basically sound system. In addition, ways should be found to cause the benefits of basic research to reach industries which do not now utilize new scientific knowledge."
17. For the list, see FDA, "Drug Products Committee Vacancies," <http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/CommitteeMembership/AdvisoryCommitteeVacancies/ucm111264.htm>.

18. For a description of its policies, see FDA, "How Drugs Are Developed and Approved," <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm>.
19. John Calfee, "FDA Advisory Committees and Conflicts of Interest: Understanding the Coinage of the Realm," *Medical Progress Today*, Manhattan Institute (October 11, 2006).
20. Peter Lurie et al., "Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings," *JAMA* 295, no. 16 (April 26, 2006): 1921–28.
21. See Troyen A. Brennan et al., "Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers," *JAMA* 295, no. 4 (January 25, 2006): 429, 431.
22. Ashley Wazana, "Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?," *JAMA* 283, no. 3 (January 19, 2000): 373–80.
23. See Paul H. Rubin, "Pharmaceutical Marketing: Medical and Industry Biases," *Journal of Pharmaceutical Finance, Economics & Policy* 13, no. 2 (2004): 65 (aware of the problem but also critical of the critics), critiquing Wazana. See also Thomas P. Stossel, "Unhealthy Opposition: The Value of Academic-Industry Relationships," *Boston Review* (May/June 2010): "The Wazana paper was a compilation of physician opinions and reports of behavior resulting from interactions with industry marketing. However, Wazana has no information about 'clinical care,' and explicitly says so."
24. FDA Advisory Committees, <http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/CommitteeMembership/AdvisoryCommitteeVacancies/ucm112954.htm>.
25. FDA, "Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers," <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM209201.pdf>.
26. For the classic exposition of the position, see Robert K. Merton, *Social Theory and Social Structure* (New York: Free Press, 1968), 588.
27. See Sheldon Krimsky, "Combating the Funding Effect in Science: What's Beyond Transparency?," *Stanford Law & Policy Review* 21 (2010): 101–23.
28. University and Small Business Patent Procedures Act, 35 U.S.C. §§ 200–212 (2006).
29. University of Chicago Statutes, Patent Policy, 18.1: "The basic policies of the University of Chicago include complete freedom of research and the unrestricted dissemination of information. Research done primarily in anticipation of profit is incompatible with the aims of the University. The normal method of dissemination of the results of academic work is through publication in scholarly or other public media. The University recognizes that in the course of research activities, some developments arise which may have commercial benefit. In order for such benefits to be realized, various steps need to be taken depending on the nature of the development. Where research or other activities carried out at the University, or with substantial aid of its

facilities or funds administered by it result in inventions, discoveries, or device-like software, such products shall be disclosed to the University, shall be the property of the University and shall be assigned to the University, or an organization designated by the University. The University, acting directly or through its designee, shall endeavor to license or assign such products in such a manner as to assure the greatest benefits to the University and the public, and provide a return to the inventor or creator. The inventor or creator and his or her Dean or other administrative head shall be consulted and kept informed of the arrangements. The conditions for the disposition of patent rights shall be consistent with (1) the basic policies of the University, (2) the terms of sponsorship of activities that led to the product, and (3) the requirements of law and professional ethics."

30. See, e.g., Office of Technology Management, University of California, San Francisco, <http://otm.ucsf.edu>.
31. University of Chicago Statutes, 18.2: "Where neither the University nor its designated organization wishes to retain the rights to the product, and the conditions of sponsorship so permit, the inventor or creator may be allowed to retain the rights, and to obtain patents or copyrights, at the expense and for the benefit of the inventor or creator, but in any event the normal processes of academic publication will be utilized for the benefit of the scholarly and general public." Clearly, this provision is not read to require prompt publication that would destroy patentability.
32. *Ibid.*
33. See <http://otm.ucsf.edu/docs/otmlPMgmt.asp#Timing>.
34. Mark H. Cooper, "Commercialization of the University and Problem Choice by Academic Biological Scientists," *Science, Technology, & Human Values* 34, no. 5 (September 2009): 629, 647.
35. For discussion, see below, n. 58.
36. Sheryl Gay Stolberg, "Institute Restricted after Gene Therapy Death," *New York Times*, May 25, 2000.
37. "Institute for Human Gene Therapy Responds to FDA," <http://www.upenn.edu/almanac/between/FDAresponse.html>.
38. Institute of Medicine, *Conflict of Interest in Medical Research, Education, and Practice*, ed. Bernard Lo and Marilyn J. Field (National Academies Press, 2009), 5.
39. The text of the provision reads: "An institutional official who holds a Board of Directors or other fiduciary position with any biomedical company, or any other company that does, or is reasonably likely to do, significant business with any Partners entity, may only retain personal cash compensation, not to exceed \$5,000 per day, equivalent to the fair market value payment, based upon time spent on Board meetings, that would be appropriate for a consulting or scientific advisory board relationship between the individual and the company. The institutional official holding the fiduciary position may not retain any equity compensation from that company for serving in that position." Partners HealthCare, "Partners Commission on Interactions with Industry," Recommendation #12 (April 2009), [http://www.partners.org/documents/CommissionReport\\_PartnersHealthCare2009.pdf](http://www.partners.org/documents/CommissionReport_PartnersHealthCare2009.pdf). For commentary, see Ed Silverman, "Boston Hospitals Limit Pharma Board Compensation," *Pharmalot*, January 4, 2010, <http://www.pharmalot.com/2010/01/boston-hospitals-limit->

pharma-board-compensation; and Duff Wilson, "Harvard Teaching Hospitals Cap Outside Pay," *New York Times*, January 2, 2010, <http://www.nytimes.com/2010/01/03/health/research/03hospital.html>.

40. Partners HealthCare, "Partners Commission on Interactions with Industry," 1.
41. *Ibid.*, 23. "The Harvard Medical School Policy on Conflicts of Interest and Commitment and the Partners Policy on Consulting and Other Outside Activities both limit faculty members [*sic*] consulting and outside activities to no more than 20% of a full-time faculty member's total professional effort. The HMS policy adds an additional, and important, further limitation that the time spent is 'not to exceed the equivalent of one working day per week.' "
42. Duff Wilson, "Harvard Teaching Hospitals Cap Outside Pay," *The New York Times*, January 2, 2010.
43. Council of Medical Specialty Societies, "Code for Interactions with Companies" (April 2010), [http://www.cmss.org/uploadedFiles/Site/CMSS\\_Policies/CMSS%20Code%20for%20Interactions%20with%20Companies%204-19-10.pdf](http://www.cmss.org/uploadedFiles/Site/CMSS_Policies/CMSS%20Code%20for%20Interactions%20with%20Companies%204-19-10.pdf).
44. Laurence J. Hirsch, "Conflicts of Interest, Authorship, and Disclosures in Industry-Related Scientific Publications: The Tort Bar and Editorial Oversight of Medical Journals," *Mayo Clinic Proceedings* 84, no. 9 (September 2009): 811–21.
45. Joseph S. Ross et al., "Guest Authorship and Ghostwriting in Publications Related to Rofecoxib: A Case Study of Industry Documents from Rofecoxib Litigation," *JAMA* 299, no. 15 (April 16, 2008): 1800. Hirsch's full account has to be read for the detailed specificity of his criticisms to be understood. See also his correction on several points of detail, "Correction to 'Conflicts of Interest, Authorship, and Disclosures in Industry-Related Scientific Publications: The Tort Bar and Editorial Oversight of Medical Journals,'" *Mayo Clinic Proceedings* 85, no. 1 (January 2010): 102, <http://www.mayoclinicproceedings.com/content/85/1/102.1.full>.
46. See reference to Hirsch's correction in preceding footnote.
47. Catherine D. DeAngelis and Phil B. Fontanarosa, "Impugning the Integrity of Medical Science: The Adverse Effects of Industry Influence," *JAMA* 299, no. 15 (April 16, 2008): 1833–35, which appeared in the same issue as the Ross et al. article condemning Merck for having "apparently manipulated dozens of publications to promote one of its products." If ever there were a topic for which full disclosure is required, this was it.
48. See David Armstrong, "The New England Journal Missed Vioxx Warning Signs" (May 15, 2006), <http://www.post-gazette.com/pg/06135/690336-114.stm>. "Internal emails show the New England Journal's expression of concern was timed to divert attention from a deposition in which Executive Editor Gregory Curfman made potentially damaging admissions about the journal's handling of the Vioxx study." According to Armstrong's reporting:

Although the New England Journal wasn't on trial for anything, the deposition produced a number of damaging admissions by Dr. Curfman. He acknowledged that neither the peer reviewers nor journal editors challenged the authors' heart-attack theory about naproxen as it was presented in the article. "Yeah, we signed off on this," he said, according to a transcript of his testimony. "And I have many times had second thoughts about having done that." ...

On the night of Dec. 7, Edward W. Campion, a senior New England Journal editor, sent a note to his staff explaining why the statement had to be released the next day. The explanation didn't involve any late-breaking information obtained by Dr. Curfman. "The reason is that tomorrow's testimony in the Vioxx trial may involve part of a deposition that Greg gave," Dr. Campion wrote. "It will be essential to notify press" about the statement "and make it prominent" on the journal's Web site, he added.

A public-relations specialist who has advised the journal since 2002 predicted the rebuke would divert attention to Merck and induce the media to ignore the New England Journal of Medicine's own role in aiding Vioxx sales.

"I believe that given what a public punching bag Merck has become, there is more than enough information and more than enough context in the statement to drive the media away from NEJM and toward the authors, Merck and plaintiff attorneys," wrote Edward Cafasso, a Boston-based public relations consultant, in a late-night email to journal staffers hours before the expression was released. Mr. Cafasso later added, "In my view, this disclosure may very well be seen as the final straw for Merck on the Vioxx matter."

As should be evident from the title, most of the article was laudatory of the *NEJM*'s exposé, taking the view that its only flaw was exposing the misleading evidence too late. At no point is it critical of *NEJM* for deviating from standard editorial practice in making serious public charges without following the requisite procedures.

49. Council of Medical Specialty Societies, "Code for Interactions with Companies" (April 2010), [http://www.cmss.org/uploadedFiles/Site/CMSS\\_Policies/CMSS%20Code%20for%20Interactions%20with%20Companies%204-19-10.pdf](http://www.cmss.org/uploadedFiles/Site/CMSS_Policies/CMSS%20Code%20for%20Interactions%20with%20Companies%204-19-10.pdf).

50. *Ibid.*, section 5.

51. John F. Duffy, "The Marginal Cost Controversy in Intellectual Property," *University of Chicago Law Review* 71, no. 1 (2004): 37.

52. For a longer discussion, see Richard A. Epstein, *Overdose: How Excessive Pharmaceutical Regulation Stifles Pharmaceutical Innovation* (New Haven, Conn.: Yale University Press, 2006), 144–53.

53. See <http://www.nccn.org/index.asp>. For my discussion of this issue, see Richard A. Epstein, "Against Permittis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs," *Minnesota Law Review* 94, no. 1 (November 13, 2009): 1.

54. For one comprehensive study, see Justin E. Bekelman, Yan Li, and Cary P. Gross, "Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review," *JAMA* 289, no. 4 (January 22, 2003): 454–65.

55. See H. Brody, "Pens and Other Pharmaceutical Industry Gifts," *American Journal of Bioethics* 3, no. 3 (summer 2003): 56; and D. Katz et al., "All Gifts Large and Small: Toward an Understanding of the Ethics of Pharmaceutical Gift-Giving," *American Journal of Bioethics* 3, no. 3 (summer 2003): 39. Neither of these short studies counts as systematic empirical evidence.

56. Bekelman et al., "Scope and Impact of Financial Conflicts of Interest in Biomedical Research," 454.

57. See Rubin, "Pharmaceutical Marketing," 65 (aware of the problem but also critical of the critics), critiquing the influential paper by Wazana, "Physicians and the Pharmaceutical Industry," which draws a similarly bland conclusion that "the present extent of physician-industry interactions appears to affect prescribing and professional behavior and should be further addressed at the level of policy and education."
58. David J. Rothman et al., "Professional Medical Associations and Their Relationships with Industry: A Proposal for Controlling Conflict of Interest," *JAMA* 301, no. 13 (April 1, 2009): 1367–68.
59. Steven Kawczak et al., "The Effect of Industry Support on Participants' Perceptions of Bias in Continuing Medical Education," *Academic Medicine* 85, no. 1 (January 2010): 80.
60. Rothman et al., "Professional Medical Associations and Their Relationships with Industry."
61. See "Partners Commission on Interactions with Industry."
62. Barbara B. Depena and Laura G. Mirviss, "Partners' Conflict of Interest Policy's Reach Concerns Docs," *Harvard Crimson*, February 19, 2010, <http://www.thecrimson.com/article/2010/2/19/policy-medical-partners-drug>.
63. Chapter 305 of the Acts of 2008, <http://www.mass.gov/legis/laws/seslaw08/sl080305.htm>.
64. Julie M. Donnelly, "Mass. Med Device Firms Hurt by Gift Ban," *Journal of New England Technology* (March 12, 2010), <http://www.masshightech.com/stories/2010/02/22/daily44-Mass-med-device-firms-hurt-by-gift-ban.html>.







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