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CONFLICTS OF INTEREST IN HEALTH CARE

who guards the guardians?

RICHARD A. EPSTEIN

ABSTRACT Conflicts of interest are rife in all areas of human endeavor, including medicine. Dealing with them is often difficult, because various disclosure remedies are sometimes too weak, while explicit prohibitions against participation in certain forms of research could block the needed synergies between scientists who work in universities, government, and industry. The situation is made still more difficult, because any effort to control one set of conflicts will necessarily generate another in its stead, as is well captured in Juvenal's famous question, "Who will guard the guardians?" That problem is more acute today, because many of our social watchdogs are in fact complex organizations that are rife with their own internal conflicts of interest. The problem is acute for the FDA, for example, which so fears the release of harmful drugs that it often keeps beneficial ones off the market. The problem can also arise in connection with the review of medical research by major journals, which is well illustrated by the recent effort of the *New England Journal of Medicine* to attack a Vioxx study it published in order to protect its own reputation.

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HOW BEST TO HANDLE conflicts of interest? That apparently innocent question raises some of the most persistent and dangerous challenges to sound management practices in health care and beyond. To get some handle on the larger topic, it is best to break it down into two related inquiries. The first asks what constitutes a conflict of interest. The second asks what, if anything, should be done to regulate or manage these conflicts once they are defined in principle and identified in practice. The difficulty of the second question is, unfortunately, made evident by the brutally simple but correct answer to the first. The proper technical definition is this: a conflict of interest arises when any individual acts in ways that will provide him with personal benefits that reduce the overall welfare of the group of which he is a part. The practical consequence is this: the expected frequency of conflicts under this definition is one. All that is needed is any transaction involving two or more people. Conflicts of interest are an inseparable feature of all cooperative human activity.

The regulation of conflicts of interest is more perilous than one would suppose, because it raises this disturbing possibility: the mechanisms that people use to control conflicts of interest—disclosure, deliberation, oversight, litigation—can never be made foolproof. The introduction of one form of intervention may have the desirable effect of eliminating some conflicts of interest. Yet at the same time, that new layer of oversight could spawn new conflicts of interest, many of which were overlooked or underappreciated when the governance structure was created. It is easy to imagine some form of infinite regress in which every reform effort to stop old conflicts creates new ones. It is far harder to guard effectively against conflicts than to identify them.

The depth of this problem is not confined to the exotic realism of modern medical practice or biochemical research, for its deep historical roots long predate the complexities of modern institutional life. In his satire *On Women*, the Roman poet Juvenal asked the question, “*Sed quis custodiet ipsos custodes?*” which is commonly translated as “But who guards the guardians?” So long as the guardian is subject to the same human weaknesses as the guarded person, the problem of misconduct is transferred but not necessarily solved. The long-standing intellectual challenge is to develop a systematic approach to minimizing the errors that crop up in oversight, which can then be carried over to designing institutions to regulate modern medical and pharmaceutical research. The first part of this essay reviews the conventional literature on “agency costs,” as the economists like to term conflicts of interest, in order to outline the deep intractability of the formal problem (for the classic discussion, see Jensen and Meckling 1976). The second part then illustrates how this issue can arise in various commercial transactions and relationships. The remaining two parts extend the analysis to the physician–patient relationship and address the relationships between physicians and drug companies.

THE INESCAPABLE ECONOMICS OF CONFLICTS OF INTEREST

The neoclassical system of economics—derived and updated from Adam Smith and the early English economic writers—starts from the simple assumption that individuals act universally to maximize their own individual self-interest. This proposition is surely overdrawn in at least two ways, neither of which defuses the conflict of interest question.

The first qualification is that individuals often seek to maximize the welfare of families and friends, so that they do not always act out of selfish motives. But in fact these limited and directed forms of altruism often *aggravate* the underlying conflicts problem—for no conflict is more acute than those that arise when individuals have, for example, dual obligations, first to their spouses and children, and second to their employers. This richer account of human psychology only adds a second layer to the conflict of interest problem. It does not remove the first.

The second qualification is that individuals do not possess the same degree of egoism. Self-interest is no different from other human traits. Some people have it in abundance and are rightly called selfish or greedy; others are considerate and aware of the needs and rights of other persons and are rightly called generous, fair-minded, or kind. In one sense, the presence of these nonselfish individuals reduces the severity of the conflicts of interest problem, for it points to some group of persons whom we can count on to rise above certain temptations. It is these people who should on average become the agents of others. Yet in another sense, the variation in egoism across individuals only makes the problem more difficult, for the responses that are appropriate to some people may not work well with others. Rules that are needed to watch over devious actors will hamstring individuals worthy of high levels of trust and independence. That variation makes it both critical and risky to slot particular individuals to particular positions. Organizations realize huge gains from a proper “fit” and huge dangers if the wrong persons are put in positions of trust. Even-handedness is a key feature in larger organizations. But what if the chosen rules stifle the freedom of virtuous individuals yet do not deter those more willing to yield to temptation? Unfortunately, it is hard to serve the twin masters of uniformity and diversity simultaneously.

CONFLICTS OF INTEREST IN COMMERCIAL TRANSACTIONS AND RELATIONSHIPS

For the moment, however, it is best to put these complications on the back burner and just approach the matter as if uniform, individual self-interest were an invariant staple of human behavior. The reason that conflicts loom so large is that in voluntary relationships, the *collective* object of the transaction is to maximize the welfare of all parties to it. Yet at the same time, the individual objective is to maximize welfare for a single person, even at the cost of some greater dislocations to one’s trading partners. In the simplest employment contract, for

example, one person agrees to perform some task in exchange for the payment of a fixed wage. The expectation is that if the work is done in accordance with contract specifications, then the wages will be paid.

If that optimistic assumption holds, each party to the relationship is better off. But the moment the deal is made, each side has a private incentive to behave strategically and thereby undermine the deal. The worker may prefer to slack off on the job, by arriving late or performing fewer inspections and checks. Or the employer may delay in paying the wage, or supply subpar equipment for doing the work. The terms of the simple employment contract may well be altered to anticipate these possibilities. One set of modest reforms is to impose penalties on late payment or performance; inspections of quality could take place; systems of payments could change from flat wages to piece work or commissions based on output and performance. Each of these devices does something to control the slack, but each imposes some cost for its execution. The two sides to an employment contract will, if rational, invest in various precautions to the point where an additional dollar in administrative expenses prevents one dollar of abuse, so that benefits and costs are equated at the margin—assuming people know where these margins lie, which often they do not.

The problems of conflict become more acute in complex organizations where individuals represent multiple parties at one time. The initial theory of labor law was that union leaders could be counted on to represent the interests of all their workers through collective negotiation with management. But bitter experience soon indicated that these leaders often advanced the interests of influential members at the expense of others, often on racial grounds, so that a duty of “fair representation” was borne to counteract that tendency (see *Steele v. Louisville & Nashville R.R.* [1944], which imposed a duty to counteract racial bias). Similar issues can arise in management teams, so that the law of corporate governance imposes the duty of loyalty on key officers and directors of the corporation, in order to reduce the risk that their self-dealing with the corporation will result in systematic losses for the firm. As the court states in *Guth v. Loft, Inc.* (1939): “The rule that requires an undivided and unselfish loyalty to the corporation demands that there shall be no conflict between duty and self-interest.”

Yet the various devices used to enforce these duties are also prey to difficulties. Disgruntled workers seeking private advantage could insist that they were subject to discrimination by the union leadership; sensible corporate transactions could be scuttled, because officers do not wish to run the risk of frivolous actions by class action lawyers. The entire process therefore shows a constant need to refine the rules of engagement to minimize the new conflicts that arise when efforts are made to counter earlier ones. After all, strike suits against corporations—whereby skilled lawyers use the threat of litigation only to extract settlement—are common against corporations. Similarly, unions have been plagued by groundless suits alleging various breaches of fiduciary duty even though it is very difficult within the framework of collective bargaining to de-

cide what wage differentials should be maintained between different skill groups. It seems fair to say that there is no clear resolution to these ubiquitous conflicts questions, even in straight business and commercial transactions.

CONFLICTS OF INTEREST IN PHYSICIAN-PATIENT RELATIONSHIPS

Financial Conflicts

The problems of conflicts of interest are especially difficult in medical matters. The most mundane form of conflict repeats the tension that is found in the standard employment contract. Suppose a patient hires a physician on a fee-for-service contract. A conflict of interest is instantly created, because the physician has a built-in incentive to recommend expensive and lavish treatments that may not be in the best interests of the patient. The fundamental difference in information levels makes it hard for patients to monitor these conflicts. So we propose a cure. The patient and physician shift to a fixed fee for all medical services. Yet lo and behold—now the same physician has an incentive to withhold services that could prove vital to patients because of the absence of any personal return to additional effort.

Since no system of payment will eliminate these conflicts, why do they not always materialize? The reputation of physicians as repeat players in the marketplace is one possible answer, for the physician who is discovered to overtreat could easily lose customers to a rival. But this incentive is highly imperfect if patient groups are diffuse, so that information travels slowly among them. Enter at this point third parties—insurers, HMOs, PPOs, and the like—who act as agents to the patients in order to make sure that unnecessary treatment is not provided. But again the two kinds of error that infect other types of transactions could easily arise here. Hence the third party could be attacked for skimping on treatment that physicians in their best medical judgment regard as appropriate for patients, regardless of cost—or is it, with cost taken into account? It may well be that these programs on average do a better job than the simple two-party relationships, as evidenced by their rapid increase in market share (AAHP 1999). But again the relationship is a halting and uncertain one, because some patients are willing to pay higher premiums as part of their basic plan in order to purchase greater freedom of choice on such crucial matters as choice of physician. Thus Preferred Provider Organizations (PPOs) permit patients to visit any doctor, but require patients to pay a higher fee for doctors outside of the PPO's network (Freudenheim 1998). The hope here is that through voluntary sorting, those business arrangements with the highest productivity garner the largest share of the market. On this view, the conflict of interest is rightly regarded as a cost of doing business for the enterprise. As such, it has to be factored into the overall accounts like any other costs. But in this translation of the underlying problem, conflicts lose their

distinctive status as a kind of ethical trump that stops all deals. Indeed in practice no other approach is possible, for in all cooperative efforts, the only question is which conflicts are best tolerated, not whether all can be eliminated.

Treatment-Related Conflicts

The conflicts of interest in medical treatment are, if anything, more profound than those that deal with the (related) financial aspects. In most standard business transactions, the parties operate on a plane in which knowledge is distributed relatively uniformly between them, so that neither side has the advantage of specialized or inside information about the underlying subject matter. That is decidedly not the case in a full range of medical and pharmaceutical transactions, where specialized and differential knowledge on medical matters is the order of the day. The simplest way to state the problem is to note that the physician (or teams of physicians) has superior knowledge on the probability distribution of outcomes (both positive and negative) of various forms of treatment, while the patient has better subjective knowledge of the values attached to these outcomes—how much he or she cares about sterility, disfigurement, etc.—than the doctor. Once that information asymmetry is recognized, the conflict of interest is acute, because the physician may attach his or her own values to these outcomes, and not those of the patient.

The key question in these cases is what institutional devices, if any, should be used to counter that otherwise decisive knowledge advantage, which is often aggravated because sick people often have dubious competence at the very moment they stand in desperate need of medical treatment. One possible response to this problem is to ban certain classes of transactions altogether on the ground that the field is just too rife for abuse. That rationale, for example, lies behind what I regard as the desperately misconceived ban on organ selling (Epstein 2006a). But while that approach might be adopted, it surely cannot be held that incompetent people are not entitled to receive medical care. Instead the old, young, and infirm are allowed, or required, to act through guardians who are chosen to have their best interests at heart. That practice works most of the time, but in some cases a parent or spouse could easily decide to prolong or terminate treatment for reasons that do not serve the best interests of the patient. Too bad: if anything, it is probably worse to allow for judicial supervision of decisions to withhold, for example, medical care to terminally ill incompetent parties. (For the unhappy experiment of judicial intervention, see *Superintendent of Belchertown State School v. Saikewicz* [1977]; for criticism, see Relman 1978. For the judicial retreat, see *Brophy v. New England Sinai Hosp., Inc.* [1986].)

Now suppose that we have competent individuals—we still have to figure out how to respond to the problem of differential knowledge. The gains from trade to both patient and physician are so great that any ban on medical transactions is literally suicidal. The early response to this paradigmatic transaction had the

physician say to the patient: “Trust me.” This is still the dominant practice in England, which resists broad legal duties of disclosure, even today (*Sidaway v. Bd. of Governors of the Bethlem Royal Hosp.* [1985]). Ideally, the patient supplies information to the physician, who then makes the right choices as a fiduciary who can rise, somehow, above his own financial interest. The system is cheap to enforce. It avoids the question of what kinds of disclosures need to be made to patients (or their guardians) in emergency situations, or when patient competence, owing to disease, age, or stress, has become questionable. But it has the defect of denying patients the right to make bodily choices on matters of far greater concern to them than to any treating physicians. Hence, the conflict of interest between patient and physician has led, quite emphatically over the past 30 or 40 years, to heightened duties of disclosure to patients (and families) about the material risks of certain kinds of treatments, with all the litigation uncertainty that this could, in some cases, create (*Canterbury v. Spence* [1972]). The theme—let disclosure be the antidote to self-interest—is one inescapable response to the problem of conflict of interest.

The doctrine of informed consent has, on balance, *not* been enforced primarily through litigation, but through social practices that bolster the duty and often lead to novel institutional arrangements (Web sites and chat groups, for example) that mean that it is no longer strictly necessary to rely on the treating physician for all relevant information. But these outside sources of information are often suspect, and in some specialized and experimental settings, an uneasy social consensus arises that the further safeguard of institutional review boards (IRBs) is needed (even in the absence of government regulation), because it is too risky for people to participate in dangerous clinical trials unless and until some independent board has reviewed the research proposal to guard against the risk that patient care will be sacrificed for a research project.

Yet consistent with the basic theme, serious dangers lurk in the wings. IRBs are a growth industry with its own bureaucracy, and they extend to any and all kinds of human subject research, including “clinical trials, behavioral research, epidemiological and survey research, outcomes research, anthropological research, educational research, field and international research, oral histories, and psychological research” (University of Chicago Institutional Review Board 2006). Yet this process raises questions of its own. It is not clear why oral histories should be subject to the same basic regime as clinical cancer trials. Nor is it easy to justify the level of coercion involved. It is one thing for each individual to receive personal advice on whether to participate in a particular clinical trial. It is quite another to endow a board to delay or block people from participating in clinical trials when they are willing to do so after receiving independent advice. Finding out who is correct is no easy matter; the IRBs (like the FDA) labor under their version of the Hippocratic rule: first do no (visible) harm. Blocking sound projects produces diffuse social losses that are hard to measure, and which in no way are chalked up to the project. But allowing projects that misfire to go

through provokes strong reactions. There are always some countervailing questions about experimental treatments, and much depends on the composition of IRBs, which could easily be staffed with experts who are so worried about the bad results that could occur if a dangerous trial takes place that they downplay the huge advances that could result from successful experimentation. So who guards these guardians, to be sure that they do not operate as an obstacle in the path of individual autonomy that can, especially in connection with social science projects (where the case for having these boards is much weaker), stifle research, resulting in adverse long-term consequences to the very groups that they want to help (for one such account, with clear First Amendment overtones, see Hamburger 2004). None of these arguments count as a knock-out punch against IRBs: individual consent is more costly and arguably less reliable than the use of this comprehensive screen. Although it is hard to generalize about the desirability of this institutional filter, one indication that such a filter might prove advantageous is that the pressure for the creation of these boards appears to come as much from within hospitals as from outside their walls. The voluntary support for these institutions counts as a point in their favor—a point, not a knock-down argument.

CONFLICTS OF INTEREST AND PHARMACEUTICAL COMPANIES

The present preoccupation with conflicts of interest reaches its most acute form with pharmaceutical companies, which have been subject to relentless public attack in recent years. In one sense, I am perhaps the wrong person to write about all these issues, because of my own conflict of interest: on a number of occasions (not currently) I have consulted for both PhRMA and Pfizer, although never on the conflict of interest issue. Nonetheless, in this case disclosure is, I think, preferable to silence, so I shall examine the pervasive conflicts of interest that give rise to such massive distrust of pharmaceutical companies.

Not surprisingly, the simplest explanation for this distrust lies in the sheer size and ostensible market and political power of the drug companies. A strong populist sentiment holds that the profit motive always corrupts the operation of large and successful firms, so that their every action must be scrutinized under the maxim that what's good for the drug company is bad for their customers and the population at large. Writ large, the position seems odd, for the number of path-breaking drugs that are routinely used to control pain and cure disease is legion. I dare say that none of the industry critics would relish a return to the halcyon days of a generation ago, so great has the overall progress been. (Readers of this journal know the particulars far better than I.) Nonetheless, progress breeds contempt, so that hostile sentiments have expressed themselves in a large number of recent books that have excoriated the industry in two key areas: their marketing practices with respect to physicians and patients, and their relationships in drug

development with the FDA and medical journals (Angell 2004; Kassirer 2004; but see Epstein 2005a, 2006b.)

As before, it is easy to identify the sources of concern: the drug company that hypes its products may be able to increase its sales and then dodge any liability from the tort system for the harms that follow. One difficulty with this indictment is that it is hard to identify which guardians should be put into place to prevent abuse. As before, it is useful to look at both the financial and medical sides of the risk.

Financial Conflicts

Marketing efforts. The chief concern in this area involves the elaborate marketing efforts that drug companies devote to new launches. The common criticism of these efforts is that companies are constantly pushing newer products under patent protection when cheaper generic products are ready and able to do the same thing. The usual account is that the marketing efforts result in heavy added costs to the consumer but do little to add benefits to the consumers to whom they are directed. The position suffers from this oddity: how can these marketing practices remain universal if they are so inefficient? Surely some firm would have found the key to success by shunning these costly maneuvers in order to grab market share and increase profits. But none has. In fact, here is a case where the practices are basically sound, and the critics, misguided. Here are some flaws in the underlying argument.

First, it should never be assumed that all advertising leads either physicians or patients down unfortunate paths. Quite the contrary—the information supplied is usually accurate and instructive, and even if inaccurate in some degree, it may represent a state of knowledge that is preferable to some general state of ignorance that it displaces. Stated otherwise, the indictment against aggressive marketing efforts would make sense if consumers and physicians were already fully informed about the pros and cons of various therapies for the full range of conditions that they treat. In the consumer markets, of course, the situation is really quite different, for many individuals, especially those of limited circumstances, are undermedicated for such common conditions as high blood pressure or high cholesterol, either because they are unaware of their own health status or because they are uninformed about the products that might do them some good. The gains from consumer advertising have to be factored into the mix.

Yet just whom should we trust to make the judgment when these gaps in consumer understanding are large enough to matter? Whatever the FDA's expertise on scientific matters, it is woefully weak on decision theory, knows little about advertisement, and seems to be oblivious to the risks of overwarning. As with every inquiry, there are two kinds of potential error: too much advertising and too little. The FDA fails to recognize that excessive restrictions on consumer advertising dampen demand and could easily delay product launch and, indirectly, long-term research. Yet who watches over the FDA? To remain in business

the drug company must generate revenues in excess of costs. With the FDA's ever-greater insistence on more clinical trials raising the break-even point for new drugs, the need for advertisement becomes greater and not less.

Second, the common attack on advertising by pharmaceutical companies assumes that consumers are constantly forced to pay for an additional expense that they don't need or want. But this argument overlooks the dynamic effects when marketing brings new customers into the fold. The key characteristic of all drug markets is high fixed costs for research and development and low marginal costs for each additional product unit. Stated in its most graphic form, it may take \$1 billion to get the first pill to market, but only \$1 dollar to get the second. A system that wants all consumers to pay only the marginal cost of the pill that they consume works wonders for patients 2 through n . But who rushes to the head of the queue to pay \$1 billion for the first pill? No one—yet the firm that cannot sell the first pill will not produce the second. The *only* way to escape this dilemma is to reduce the cost of the first pill, which means that those lost revenues are only recouped by charging over \$1 for subsequent pills. The marketing expenses that increase the total costs of production also increase total demand for the pill. As more people purchase the pill, this reduces the *average* cost per pill, and thus benefits, not harms, consumers. Obviously, it is possible to have too much or too little advertisement, but it is not credible to think that any government agency with a puritanical bent could identify the ideal level. The best restraint on a given firm is competition from other goods, which will only take place if they too may advertise their wares.

Similar arguments hold, I believe, with respect to the strenuous marketing campaigns that drug companies undertake to the medical profession. Initially, it is always somewhat odd for experienced professionals to claim that they are easily duped or seduced by bloated claims of drug companies. And the surveys that purport to show that often do no such thing. (See Wazana 2000 [an expose of industry practices], but also Rubin 2004 [aware of the problem, but also critical of the critics].) To be sure, some physicians may have poor judgment and fail to critically evaluate drug-marketing campaigns. As before, the key question is whether even partial information from one drug company is better than no information at all. Even more than in consumer markets, the downside is limited, both because drug marketers compete with each other and because of the mass information that comes from independent sources, often professional in nature, both pre- and post-release. Set in context, the ultimate issue is whether there has been any reduction in the quality of patient care, which is an elusive variable that none of the studies have been able to measure.

Once the complexity of the multiple effects is realized, then we should be cautious about jumping to conclusions on the proper remedy for various sorts of ills. In this regard, I take exception to the proposal that Dr. Troyen Brennan, then of Harvard School of Public Health (but now Chief Medical Officer of Aetna), and other prominent leaders of academic medicine made with respect to

these potential conflicts of interest. In their view, disclosure of conflicts of interest is hardly sufficient to tame the marketing tiger. But it does not follow that one has to leap to the opposite direction, whereby academic medical centers unilaterally adopt overly strict conflict of interest rules, including bans on any kinds of gift to physicians, the refusal to take free samples from companies (which are often distributed to needy patients), and the refusal to allow any staff physician to sit on formulary committees if they have any connection with drug companies (Brennan et al. 2006; but see Stossel 2005). Although these autonomous institutions should be allowed to adopt whatever rules of internal governance they choose, the wisdom of this blunderbuss approach may properly be called into question.

And for good reason. Staffing formularies only with independent physician runs the risk of both ignorance and bias. The strong prohibition will deprive these committees of some of their most dedicated members, whose information base may not be replicated by physicians who lack these connections. Worse still, a formulary committee without industry representatives may be subject to prejudices of its own: hostility to for-profit pharmaceuticals could lead them to reject new patented drugs of greater efficacy than inferior generic products, for example. On balance, it is unwise to staff any general committee solely with individuals who have, or don't have, drug company connections. But the optimal mix may well include (in addition to other types of specialists, like administrators) both sorts of physicians. Their complementary skills could easily be greater than those skills found in committees staffed exclusively by individuals cut from one mold. Disclosures are still required, and individuals—from either camp—should abstain from those cases in which they have a direct interest in a particular drug or device, and perhaps even (depending on local circumstances) when any product of a related company is under consideration. But the meat cleaver of total exclusion is too blunt an instrument for conflicts. The information gained from a wider range of perspectives can in many cases overcome the risks. And the institutions that try to have all guardians guard each other are likely to do better than those that regard certain classes of individuals beyond the pale. As ever, any conflict imposes costs. But in many settings their costs are outweighed by other distortions brought about by supposedly prophylactic rules.

The NIH conflict regulations. A similar pall over conflict regulations has developed within government research laboratories, where the fear of conflicts of interest has led to some harsh regulations intended to curb the problem (NIH 2006). In their current form, these regulations prohibit compensated employment, including consulting and advisory or other board service, and compensated teaching, speaking, writing, or editing for a wide range of biotech, pharmaceutical, hospital, HMOs, and educational and research institutions that had recent NIH grants (5 C.F.R. § 5501.109(c) [2006]). There is no effort to take into account the circumstances of individual cases. The rule in effect will kill all conflict but it will also kill all sorts of gainful cooperation as well, and there is

no willingness to take into account any adverse impact that these restrictions will impose on other organizations whose ability to attract top talent is limited by the regulations. The point here is of great importance. One of the major challenges in scientific research is to ensure the orderly transmission of public information to firms that specialize in proprietary information protected either by patents or trade secrets. In making this transition more painful and uncertain, we reduce the long-term value of both basic and applied research. The guardian thus inflicts substantial system-wide costs in the effort to cleanse its own house.

Where's the hidden conflict of interest? The NIH does not think that it is in a strong enough position to protect its own appropriations and position in the face of scandals or irregularities. It is evident that it does not think that the faithful enforcement of its own previous rules could protect itself. Hence it sacrifices the orderly interchange of scientific information across institutions in order to insulate itself from charges of irregularities. In this, of course, it is not alone. Much of the objection to the stringent FDA rules stems from just this source. Visible harm creates political risks that indirect social losses do not. The do no (visible) harm rule represents an improper institutional response to its own conflict of interest problem, which by chilling collaboration does far more damage than the occasional consultation arrangement that would not be caught by the less restrictive conflict of interest rules in place before the recent NIH edict.

Scientific Matters

Which drugs should reach the market? The dangers of overregulation of conflicts of interest are also evident in dealing with sensitive scientific information. As with all social situations, we must be on guard against two forms of error: letting drugs into the marketplace that are too dangerous, and keeping out those drugs that are on net beneficial. In my own view, the first of these risks is less critical than the second. Letting drugs be sold is, for example, consistent with requiring that a patient receive a prescription, because there is a second line of defense that could stop erroneous use even if the first line of defense is breached (Epstein 2005b).

Note this second line of defense is all the more critical because of the simple truth, often overlooked by the FDA, that variation in drug response necessarily means that products that are harmful to some may prove helpful to others. If physicians had no means in advance to measure this variation in response (by offering low doses to test tolerance, or by other forms of testing), then all persons would have to be treated as though they were located at the mean, so that a collective determination, up or down, would start to make some sense. But in fact rough segmentation is available in advance. Precisely because physicians and other persons use drugs once they are released into the marketplace, the tough FDA scrutiny unwisely prevents people who could really benefit from certain drugs from using them. The guardianship relationship poses the same conflict of interest problems found in other contexts. The principle of do no (visible) harm means

that it is in the FDA's interest, along with those in Congress who exercise oversight functions, to err in favor of keeping too many drugs off the marketplace.

NEJM and Vioxx. The FDA is not the only organization that has to deal with conflicts issues in drug testing. The effort to gain recognition and advancement in medicine means that individual scientists could easily engage in forms of scientific misconduct that allow for their own personal advancement. The issue of conflict of interest is in this context intimately tied to the question of academic fraud—the deliberate misstatement or trimming of data and results for personal advancement. How then to deal with this situation? This issue is one on which I played an active role in the mid-1980s as the principal draftsman of the University of Chicago's rules that dealt with the topic (Epstein 1986). One central conclusion that arose from the University's internal deliberations on this topic was the importance of formal procedures to make sure that both sides were heard in all cases. The stakes—academic excommunication and public humiliation—are so high that no informal procedures that depend on the good will of panel members can control the high risk of abuse. One of many reasons for this sensitivity is that the potential conflicts of interest that can arise in the evaluation of work when priority of discovery is often a key issue.

The demand for formal procedures to control against conflicts of interest does not only apply to universities that house scientists, but also to the academic journals that routinely publish the results of clinical trials. Such journals are rife with the risk of conflict of interest, since they are supported by the same drug companies that desperately seek FDA approval for products. Figuring out who guards the guardians remains a challenge. The best illustration of this problem are the serious charges that the *New England Journal of Medicine* (NEJM) made against both the independent scientists and the Merck scientists who published a study on the effects of Vioxx on both cardiovascular and gastrointestinal risks. The matter came to a head in December 2005, when the NEJM published “an expression of concern” with respect to a clinical study that had appeared in its pages (Curfman, Morrissey, and Drazen 2005). The term “expression of concern” is itself a somewhat obscure technical phrase for a charge of academic fraud. The substance of the initial set of charges was that Merck had not reported three adverse events from the trial, which had been conducted on a double-blind basis at multiple research sites in the United States and abroad. In addition, the expression of concern stated that certain tables had been deleted from the original study before it was published.

In this context, I will not address any of the underlying issues of liability (on which I think that Merck should have powerful defenses—Epstein 2006b, pp. 208–16). Nor for the moment, at least, shall I address the substantive merits of the liability case against Merck. Instead I shall begin with the guardianship question of conflicts of interest. The International Committee of Medical Journal Editors, whose standards the NEJM follows, has developed specific procedures for handling cases of scientific fraud. These standards state that “it is the editor's respon-

sibility to ensure that the question is appropriately pursued, usually by the authors' sponsoring institution" (ICMJE 2006). What is most striking on the procedural front is that the *NEJM* did not follow that procedure at all, but published its expression of concern after a brief internal discussion, without giving any of the accused authors an opportunity to present their side of the case in private before publication. At the time, several bloggers noted that this seemed an odd procedure given that the expression of concern was published over 14 months after Vioxx had been withdrawn from the market (Hu 2005; Lowe 2005).

It turns out that the conflicts of interest for the *NEJM* were acute in this case. A comprehensive story on the matter in the *Wall Street Journal* noted that the editors of the *NEJM* had been caught flatfooted in depositions on the Vioxx litigation conducted by plaintiff's attorneys. As the story is retold in the *Wall Street Journal*: "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" (Armstrong 2006). The higher-ups were distressed that the pending litigation would focus its attention on the inability of the *NEJM* to spot errors in the Vioxx study, which would in turn damage its reputation in medical circles. In order to block this reputational hit, the senior editors decided to launch a preemptive strike against Merck. On the evening of December 7, 2005, they announced to the Journal's staff that they were going to post the expression of concern on the *NEJM* Web site the next day, just before a Vioxx trial was scheduled to begin in Houston. In following this course, they consciously chose not to follow the usual procedures, which would have required the matter to be referred to 13 universities and of course to Merck, which employed two of the key scientists who were involved in the project. The conflict of interest between the reputational hit to the *NEJM* and the extension of elementary rights of hearing and notice to authors tagged with very serious public charges seems painfully evident. Yet in response to the *Wall Street Journal* article, Jeffrey M. Drazen, the Editor-in-Chief of the *NEJM*, did not address the real source of discomfiture, but only noted that the *NEJM* cannot be required to conduct individual investigations of all submitted articles (Drazen 2006). True, but beside the point. Once again, who guards the guardians?

In general, when procedures are shoddy, the substantive results are usually incorrect as well. That appears to be the case here. The drift in the *Wall Street Journal* article was that *NEJM* editors feared that they would be castigated for "lax" editing. The article contained no substantive examination of the charges contained in *NEJM*'s expression of concern or the responses to them. I have looked at all the available published materials, and I think that it is beyond reasonable doubt that the *NEJM* charges were more than answered by the Vioxx scientists (Bombardier, et al. 2006 [response by the 11 independent scientists who participated in the VIGOR study]; Reicin and Shapiro 2006 [response by the two Merck scientists who participated in the study]). In response to the charge that

the authors did not include the adverse events reported after the paper was submitted, the authors noted that they had simply adhered to a predetermined cutoff date, which had been set up in order to facilitate the publication—a common practice, which is often not reported in papers (Wadman 2005). In response to the charge that that several tables had been deleted, the authors' response was that the tables were empty, that the *NEJM* editors limited the number of tables that could be included in any article, and that no data were changed. The *NEJM* was not deterred but published a short reaffirmation of its expression of concern, which did not correct its original error but instead asserted two new grounds for its unhappiness (Curfman, Morrissey, and Drazen 2006). The first, of no consequence, is that the pre-specified cutoff date was not mentioned in the study. It is hard to see why this rises even to the level of negligence when such procedural information is routinely omitted from studies. The second, which requires a bit more comment, was that the endpoint for the cardiac portion of the study was a month earlier than that for the gastrointestinal portion of the study, which the *NEJM* claimed "inevitably skewed" the results. Wrong, on at least two grounds. First, the different cutoff dates, both approved by an independent oversight committee, were done to allow extra time to assemble the more complex cardiac data. Second, and more critically, the outcomes could not have been skewed, because none of the participants had any knowledge that would allow them to infer that the data would look better or worse if either the earlier or later date had been chosen ahead of time for both parties of the study—a conclusion that remains true even if the cutoff dates were chosen the day before the double-blinded studies were brought to an end.

The lesson here is one that has to be learned over and over again. The conflict of interest question does not mix well with absolute bans, which kill useful cooperation. But once the ban is rejected as the dominant instrument of social control, then substantial resources have to be invested in policing these conflicts of interest to make sure that they do not get out of hand. One reason why it is appropriate in this context to make constant refrains to the rule of law is that sound administrative procedures are a minimum condition for success, for only these can block the rush to judgment that marred the *NEJM*'s handling of the entire Vioxx matter. Who will guard the guardians? It is as tough a question for us as it was for Juvenal.

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