FOREWORD

"Institutional Corruption" Defined

Lawrence Lessig

Kindergarten ethics sees the world in black and white. There are good people. There are bad people. Good comes from the former, bad from the latter.

But to grow up is to recognize that such simple links simply do not hold. There is bad produced by bad souls – there are people who forge data or who lie on grant applications. But not all bad comes from the bad acts of bad souls. Indeed, sometimes perfectly decent souls intending the very best for all nonetheless produce harm. How a society or legal system reckons and avoids such harm is the difficult work of any system of institutional ethics.

The field of "institutional corruption" was launched to help ethics grow up. As ethicists, we needed to think about the ways in which systems of incentives, or economies of influence, might advance or deter a collective objective. Or the ways in which a person with the very best intentions might behave within a system that nonetheless defeats what that person understands the institution's goal to be.

One metaphor for this type of corruption is the idea of magnetic deviation. Think of a compass whose arrow is pointing towards magnetic north, then imagine a magnet drawn close to the compass. The magnet draws the arrow away from the direction in which it was designed to point.

That deviation in a literal sense is a kind of corruption. And if we translate that sense of corruption to institutions, a working definition of "institutional corruption" might be this:

Lawrence Lessig, J.D., M.A., *is the Roy L. Furman Professor of Law and Leadership at Harvard Law School. He is also the Director of the Edmond J. Safra Foundation Center for Ethics.*

Institutional corruption is manifest when there is a systemic and strategic influence which is legal, or even currently ethical, that undermines the institution's effectiveness by diverting it from its purpose or weakening its ability to achieve its purpose, including, to the extent relevant to its purpose, weakening either the public's trust in that institution or the institution's inherent trustworthiness.

There are a number of subtleties in this definition that it is useful to highlight.

- **"systemic and strategic influence":** There are plenty of influences that weaken an institution's effectiveness or performance. Laziness, for example. But we are not interested in every source of inefficiency. Our focus is upon a subset of those inefficiencies: influences that are systematic – meaning regular and predictable – and strategic – meaning used by others to achieve the deviation identified. The most common of such influences is money, but that is not the only one. Ideology within a judiciary could be a form of institutional corruption, even without money changing hands.
- **"which is legal, or even currently ethical":** The aim is to distinguish institutional corruption from other more familiar forms of corruption. This definition therefore excludes those more familiar forms. And "currently" signals that, as the institution is currently regulated, the influence may well be permitted, but that recognition of this kind of corruption might bring about a change in regulation.
- **"undermines the institution's effectiveness":** The definition is consequentialist: the touchstone of institutional corruption is an effect that the corrupt behaviors have.

- **"by diverting it from its purpose":** One possible consequence of institutional corruption is that the institution is incapable of achieving its purpose. But the definition does not purport to specify the institution's purpose or even to presume that any particular institution has a purpose. If an institution does not have a purpose, then it cannot be corrupted in this sense. If it does, then corruption is manifested relative to that purpose.
- **"or weakening its ability to achieve its purpose":** This specifies a weaker type of deviation by which the influence makes it more difficult for the institution to achieve its purpose. This, in turn, suggests that the institution might sometimes deviate from its purpose, due to the corrupting influence, and sometimes not. Consider again a judiciary that had been corrupted by ideology: many cases will not involve ideological questions and for those, there would be no deviation. But for cases that do involve ideology, there would be deviation relative to the ideals of a judiciary.
- **"including, to the extent relevant to its purpose":** Some cases of institutional corruption will involve the public's trust in an institution. This part of the definition is therefore technically redundant, but is provided to guide a research program to focus explicitly on ways in which the trust in – or trustworthiness of – an institution is reckoned.
- **"weakening the public's trust":** Some institutions, such as the institution of public health, require that the public trust its recommendations. Influences that make it more difficult to trust the recommendations of the institution are therefore corruptions of it.
- **"or the institution's inherent trustworthiness":** Trustworthiness points to the independent indicia of trust in an institution, which operate to give people reason to trust it. Institutional corruption can operate on these, too.

There are also a few features of the definition as a whole that it is useful to identify explicitly.

First, the definition is institution-agnostic: one could as well describe the institutional corruption of the Church as of the Mafia. The definition itself doesn't purport to say which corruption is worse, even though ordinary moral notions would suggest that the corruption of the Church is a bad thing while the corruption of the Mafia is not.

Second, the definition does not purport to make an "overall" judgment: to say that an influence corrupts an institution does not on its own say whether that influence should be stopped or regulated. First, the benefits of such "corruption" could well outweigh the costs. Similarly, the costs of reforming such "corruption" could outweigh the benefits. The definition does not purport to resolve whether either condition is true and, in either case, a consequentialist would see little reason to intervene.

Third, though an influence may "corrupt" an institution, that corruption may well serve a legitimate end. The *Washington Post* "corrupted" the Nixon presidency. That is, the newspaper's reporting weakened the effectiveness of that administration and undermined the public's trust in it. But few (save perhaps Nixon) would condemn such a corruption. It was fully justified by the larger ends of democracy.

These examples highlight a repeated reservation about using the term "corruption" to describe the deviation, or misaligned incentives, that we are focused upon: If it's not obvious that an influence identified as corrupting should be stopped, or should even be condemned, why deem it "corrupt"? Why not reserve the term "corruption" for unambiguously wrong influences by building into the definition the normative conditions that would distinguish bad corruption from good corruption?

But this returns us to the point that opened this essay. While the field of ethics helps arbitrate between good and bad, it does not follow that the analytical tools we use must embed that normative judgment. Demand and supply curves help explain criminal as well as ethical behavior. Nothing in ethics should ban

The field of "institutional corruption" was launched to help ethics grow up. As ethicists, we needed to think about the ways in which systems of incentives, or economies of influence, might advance or deter a collective objective. Or the ways in which a person with the very best intentions might behave within a system that nonetheless defeats what that person understands the institution's goal to be.

a tool merely because it does not try to separate good demand or supply from bad.

Keeping a broader focus, moreover, permits the development of a more robust analysis. Perhaps there is something to learn about the corruption of auditing by understanding better the corruption of the Mafia. There is no guarantee of such a benefit, but in my view, the possibility should be kept open. If we are successful, then the tools we develop will make it easier to identify and remedy strategic influences intended to deflect an institution from its objective. And I am quite confident that those tools will be used where the corruption at issue is the sort a decent society would want to end. But developing the necessary analytic tools to identify "institutional corruption" does not require us to limit the population of instances of "corruption" to that subset we want to remedy. The analytic work is distinct from the normative work. My aim here is the former.

The essays collected in this volume are a first contribution applying this methodology to the pharmaceutical industry. Every author in this collection writes from the perspective of institutional corruption. Not every author accepts the definition that I have offered here, or at least, not completely. But a field does not begin with a definition. It begins with examples and with analysis of those examples. And the collection offered here is a rich and valuable intervention into a field that is increasingly the focus of regulators and the public.

My hope is that this collection might inspire a similar examination elsewhere. For however familiar are the views of some that the pharmaceutical industry's influence on medical practice and public health is an example of institutional corruption, I am convinced there are many other examples even more significant to the public good. Seeing the dynamic of institutional corruption in both a context familiar to the reader as well as unfamiliar is essential to understanding it completely. It is also essential to developing a full range of useful remedies wherever institutional corruption is encountered.

Spending on Consumer Advertising for Top-Selling Prescription Drugs in U.S. Favors Those With Low Added Benefit

Analysis also revealed that majority of top-selling prescription drugs in the U.S.—more than two-thirds—are rated as having low added benefit compared to other drugs

Published **February 07, 2023**

DRUGS

A new study led by researchers at the Johns Hopkins Bloomberg School of Public Health found that the share of promotional spending allocated to consumer advertising was on average 14.3 percentage points higher for drugs with low added benefit compared to drugs with high added benefit.

The analysis also revealed that the majority—68 percent or 92 of the 135 drugs included in the analysis—of the top-selling prescription drugs sold in 2020 were rated as offering low added benefit. The U.S. does not currently assess prescription drugs for comparative effectiveness. The researchers based their rating categories on France and Canada's ratings of the same prescription drugs sold in the U.S., some under different brand names.

Johns Hopkins University

Johns Hopkins Bloomberg School of Public Health

The findings, published online in *JAMA* on February 7, highlight the complex dynamic between consumer advertising for prescription drugs and patients and clinicians. The U.S. is the only country besides New Zealand that allows direct advertising of prescription drugs to consumers. In the U.S., this includes digital, magazine, newspaper, billboard, radio, and television promotion.

Previous research suggests that direct to consumer advertising (DTCA) is associated with increased patient requests for advertised drugs and the increased chance that clinicians will prescribe them. Patient requests for advertised products may present an opportunity for discussing treatment options. At the same time, this may create a burden for clinicians and potentially lead to tension or distrust if the patient requests are not met.

“The findings suggest that shifting promotional dollars to direct-to-consumer advertising potentially reflects a strategy to drive patient demand for drugs that clinicians would be less likely to prescribe,” says Michael DiStefano, PhD, assistant scientist in the Bloomberg School’s Department of Health Policy and Management and lead author of the study. “When a consumer sees these advertisements on TV or social media, they should really question if it’s the best drug for them and have a conversation with their provider.”

Since 1996, annual direct-to-consumer advertising budgets for prescription drugs have increased from $1.3 billion to, in 2016, $6 billion.

The study drew from IQVIA databases that report national sales estimates and promotional spending for pharmaceutical drugs. The analysis focused on 134 of the 150 top-selling branded prescription drugs in 2020. These 150 drugs represented 60 percent of all U.S. drug sales in 2020. Sixteen drugs were excluded from the primary analysis due to missing data. The percent of total promotional spending allocated to DTCA for each product was computed.

France uses five possible ratings for added benefit—major, important, moderate, minor, and none. Canada uses four categories—breakthrough, substantial, moderate, slight/none. The ratings are based on clinical research. For their rating categories, the researchers aggregated the top three ratings into “high added benefit” and the remaining ratings into “low added benefit” from France and Canada’s ratings. Both countries use their ratings to inform pricing.

The analysis used France’s ratings for 108 drugs and, when there were no French ratings, Canada’s ratings for 26 drugs.

In addition to promotional spending and added clinical benefit, the researchers analyzed data on the health condition being treated, how the medication is administered, availability of a generic option, year of FDA approval, Medicare spending per beneficiary, and other drug characteristics.

The study found that the median promotional spending per drug in the study sample, including to patients and clinicians, was $20.9 million in 2020. The median spending per drug on direct-to-consumer advertising was 13.5 percent of promotional budgets.

The researchers also found a large variation of spending on direct-to-consumer advertising among the prescription drugs analyzed in the study. Manufacturers of six of the best-selling drugs spent more than 90 percent of their promotional budget targeting consumers versus clinicians. These drugs include treatment options for motor neuropathy, various cancers, including breast cancers, multiple sclerosis, and HIV. Drugs treating metabolism and the digestive tract had a significantly lower share of total promotional spending on direct-to-consumer advertising.

The authors note that the study has several limitations. It only looked at one year. The data did not capture certain promotional elements, including patient coupons and other promotions. France's and Canada's ratings systems may reflect different value judgements.

"This comes down to a consumer issue, not necessarily a policy issue," says Gerard Anderson, PhD, professor in the Department of Health Policy and Management and senior author of the study. "Another consideration is the U.S. doesn't currently rate prescription drugs. Imagine if the drug ads you saw on TV were required to tell you how well the drug performed against alternative drugs for the same disease. That might change how interested you would be in the drug."

"Association Between Pharmaceutical Product Characteristics and Manufacturer Spending on Direct-to-Consumer Advertising" was written by Michael DiStefano, Jenny Markell, Caroline Doherty, G. Caleb Alexander, and Gerard Anderson.

The study was supported by Arnold Ventures and the Agency for Healthcare Research and Quality (Grant #T32HS000029).

Authors' Disclosure: Co-author Caleb Alexander, MD, MS, is past chair and a current member of the Food and Drug Administration's Peripheral and Central Nervous System Advisory Committee; is a co-founding principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation, for whom he has served as a paid expert witness; and is a past member of OptumRx's National P&T Committee.

# # #

Media contacts: Caitlin Hoffman at choffman@jhu.edu (mailto:choffman@jhu.edu) and Kristine Henry at khenry39@jhu.edu (mailto:khenry39@jhu.edu).

Corruption of Pharmaceutical Markets: Addressing the Misalignment of Financial Incentives and Public Health

Marc-André Gagnon

The Disconnection between Health Ethics and Business Models

This article argues that the misalignment of private profit-maximizing objectives with public health needs causes institutional corruption in the pharmaceutical sector and systematically leads firms to act contrary to public heath. The article analyzes how financial incentives generate a business model promoting harmful practices and explores several means of realigning financial incentives in order to foster therapeutic innovation and promote the rational use of medicines. These means are:

1. Fines and criminal penalties for illegal conduct.
2. Tax policy to promote specific corporate activities.
3. New forms of prescription drug pricing, such as reference-based pricing (RBP) and value-based pricing (VBP).

Over the last two decades, the dominant business model of major pharmaceutical companies has been characterized by massive spending on promotion. In particular, there has been an explosion of pharmaceutical promotion directed towards physicians.[1] At the same time, little therapeutic innovation has been coming out of these firms' research labs.[2] According to Bill Burns, chief of Roche's pharmaceutical division, the dominant business model in pharmaceuticals can be characterized as the "me-slightly-different-marketed-like-hell" model.[3] It is a model based on the overpromotion of blockbuster drugs, many of which do not even provide any therapeutic advance.[4]

Drug promotion is not objectionable per se if its use simply disseminates information and evidence in order to promote the rational use of medicines. But in fact, it regularly involves illegal off-label promotion of prescription drugs,[5] kickbacks and financial incentives to influence physician prescribing,[6] and the dissemination of biased information to health care professionals.[7] This state of affairs should not be surprising if we look at the economics of this sector. While drug companies supply new medicines, demand comes from physicians prescribing products without paying for them. This is one of the rare economic cases

Marc-André Gagnon, Ph.D., *is an Assistant Professor at the School of Public Policy and Administration at Carleton University (Ottawa, Canada). He holds a Ph.D. in political science from York University and a Masters of Advanced Studies in Economics from École Normale Supérieure de Fontenay/St-Cloud and Paris-I Sorbonne and was a research fellow with the Edmond J. Safra Center for Ethics at Harvard University from 2010 to 2012.*

in which demand has no budget constraints. It was estimated that, in the United States, the pharmaceutical industry spends up to $42 billion in promotion towards physicians every year, which is, on average, $61,000 per physician to influence their prescribing habits and generate profits.[8]

Moreover, a growing body of evidence demonstrates that promotional activities are not confined solely to marketing, but are becoming an integral part of how medical research is being organized in the private sector. Research and development are often organized to create a sales argument for drug representatives in order to increase the sales of products with little therapeutic benefit and sometimes with undisclosed adverse effects.[9] This dominant business model relies on several corporate strategies, including systematic ghostwriting and publication planning,[10] leveraging systemic conflicts of interests of key opinion leaders,[11] seeding trials designed to introduce a new product instead of testing a scientific hypothesis,[12] failing to disclose negative results from studies,[13] and sometimes even bullying independent researchers who arrive at unfavorable conclusions.[14]

It is of little use to blame the pharmaceutical companies for lacking corporate social responsibility if current financial incentives promote such practices. In fact, because these incentives are systemic, the concept of institutional corruption[15] can be used to describe the dynamics of influence at work in the drug industry, leading the institutions underpinning medical research and physicians' prescribing behavior away from their ethical purposes, even when quid pro quo corruption itself is not involved.[16] To tackle this problem, then, one must change the systemic financial incentives at work.

Pharmaceutical Markets and Financial Incentives

Pharmaceutical markets are among the most regulated markets. Regulations oversee how drugs are discovered, produced, marketed, and dispensed.[17] A set of institutional devices supports investment in pharmaceutical research and development, including patent protection, data exclusivity, tax credits, special programs to support research for orphan drugs, and state financial incentives to promote business-university partnerships. The sale of pharmaceutical products is also heavily regulated, with an approval process requiring a series of clinical trials to prove that the product is nontoxic and that it provides greater benefit than a placebo. Most pharmaceutical products can be accessed only with a prescription from a health care professional and must be dispensed by a pharmacist, each following an extensive set of regulations governing their respective professions. The content of pharmaceutical advertising, both to professionals and to consumers, is also heavily regulated.

Physicians' indifference to price when prescribing pharmaceutical products makes them profitable targets for promotion. Furthermore, when patients buy pharmaceutical products, they rarely pay the full price themselves. Drug coverage is often provided through third-party payers: insurance companies in the case of private health benefits (normally negotiated collectively by employers) or the state in the case of public drug coverage. Most drug coverage systems specify which drugs will be reimbursed; for example, by managing drug formularies or by requiring substitution when generic products are available. Drug pricing and reimbursement varies greatly from one country to another, with most countries using some form of price regulation for prescription drugs.[18] For many drug plans, health technology assessment — comparing drug costs with therapeutic benefits — has become

It is of little use to blame the pharmaceutical companies for lacking corporate social responsibility if current financial incentives promote such practices. In fact, because these incentives are systemic, the concept of institutional corruption can be used to describe the dynamics of influence at work in the drug industry, leading the institutions underpinning medical research and physicians' prescribing behavior away from their ethical purposes, even when quid pro quo corruption itself is not involved. To tackle this problem, then, one must change the systemic financial incentives at work.

central in determining the price of pharmaceutical products and establishing the modalities for access and reimbursement.[19]

Pharmaceutical markets can be compared to a dinner for three: the first person (the physician) orders the meal (from a heavily regulated menu), the second person (the patient) eats it, and the third one (the third-party payer) pays for it.[20] While the third person might want to have a say about which meal is being ordered, the waiter is pretty aggressive in promoting the newest (patent-protected) meals — which also happen to be the most expensive.

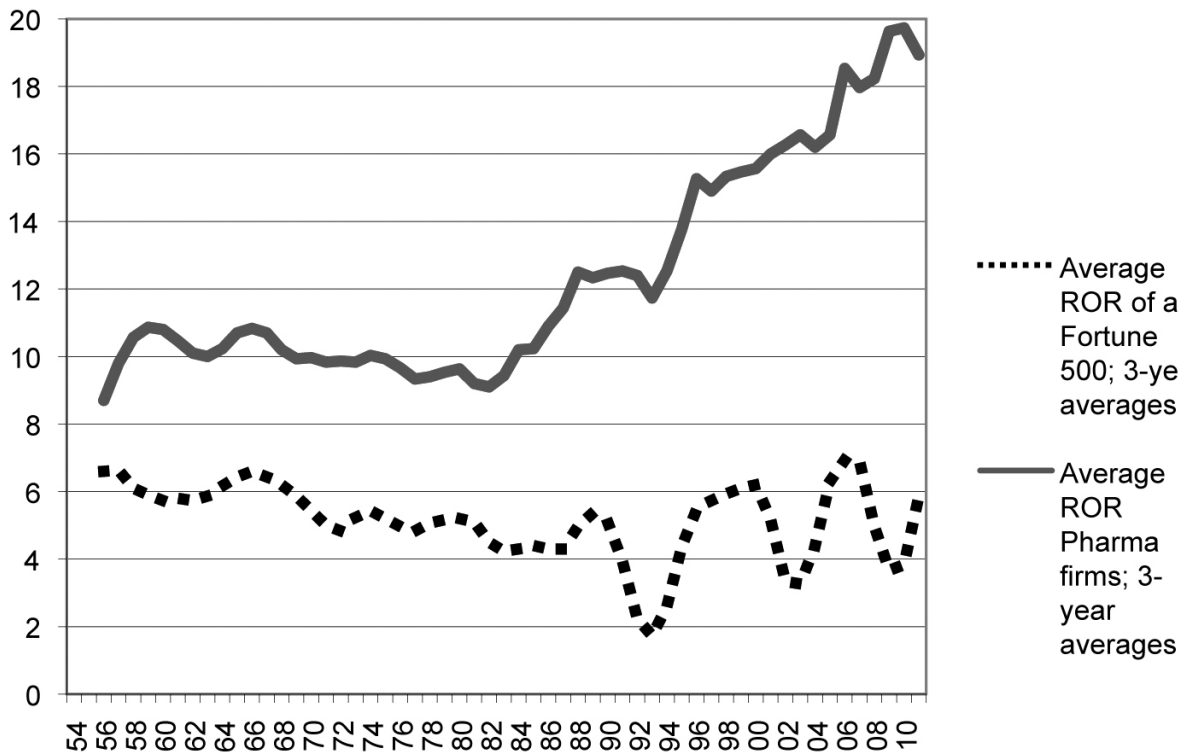
Pharmaceutical firms not only produce new medicines, they also help shape demand and the rules of the game in several ways. For example, they engage in massive lobbying to extend patent protection,[21] increase tax credits, reduce the standards in the drug approval process, and maintain secrecy over clinical trial data. The major pharmaceutical firms, like the dominant corporations in any industrial sector, use their concentrated private power to influence the political process in order to shape markets in accordance with their economic interests. Through massive marketing and promotional campaigns, drug firms also shape and intensify the demand for their products.

The dominant pharmaceutical business model can increase a firm's earning capacity by distorting medical research and medical practice. Objectionable corporate strategies are the product not of rogue corporations, but rather of systemic market incentives. Individual companies are left with little choice but to use these objectionable practices in order to survive in the corrupt market structure.

The importance of institutional corruption in the pharmaceutical sector can be easily established: in the last 20 years, fewer new molecular entities (compounds without precedent among regulated and approved drug products) have been launched on the market every year,[22] with the vast majority of new drugs offering little or no therapeutic advance over existing products.[23] The National Institute of Health is addressing the innovation crisis, in part by creating a major public research lab to develop new drugs.[24] Nevertheless, dominant pharmaceutical companies

Figure 1

Net Return on Revenues (ROR) of an Average U.S. Major Pharmaceutical Company Compared with That of an Average Fortune 500 Company (1954-2011, three-year averages)



Source: *Fortune* 500 database[25]

continue to make record profits in spite of the lack of therapeutic innovation. Figure 1 shows the evolution of profit rate for major U.S. pharmaceutical companies compared with that of major U.S. companies in other sectors.

If we keep in mind the context of the innovation crisis since the 1990s, Figure 1 shows clearly that a pharmaceutical firm does not need to come up with new beneficial drugs to increase its earnings. In fact, it becomes clear that the profit motive in the pharmaceutical sector does not encourage the development of new drugs as the main way to increase earning capacity. One can thus infer that the industry's business model does not rest on therapeutic innovation and the rational use of medicines and might instead rest on the institutional corruption of medicine through the further entrenchment of harmful practices.

This business model encourages physicians to prescribe newer and more expensive products that may provide less therapeutic benefit or inflict more harm than older and cheaper products. For example, the new generations of antihypertensive drugs[26] and antipsychotic drugs[27] are dominating their respective markets despite being less efficacious and more expensive than older generations of those drugs. Furthermore, for 70 percent of patients taking antidepressants, the drug has been shown to be no more efficacious than a placebo.[28] Another example is that, for decades, the industry has used ghostwriting and the nondisclosure of negative studies to promote the widespread prescription of hormone replacement therapy during menopause in spite of significant adverse effects outweighing the benefits of the treatment.[29] It appears that physicians' prescribing habits are informed not only by clinical evidence, but also by marketing and by the corruption of science, both in terms of lavish promotional campaigns and ghost management of medical science.[30] In many ways, one can say that evidence-based medicine has been replaced by a marketing-based medicine in which research is often organized to provide tailored truths for marketing purposes.[31]

In the United States, authorities have already started to react to the institutional corruption of the pharmaceutical sector. For example, in 2008, Senator Charles Grassley (R-IA) investigated ghostwriting and illegal promotion. Since 2007, all clinical trials are required to disclose their protocols and results in a national registry in order to reduce the systematic selective reporting of clinical trial results. Some states now require the full disclosure of every payment received by physicians from drug companies. While these reforms increase transparency, they do not change the institutional architecture of the market and therefore do not change the dominant business models.[32] The roots of institutional corruption lie first and foremost in the fact that financial incentives are misaligned so as not to drive companies to achieve optimal health outcomes. This problem must therefore be tackled by transforming the financial incentives. Three potential solutions can help reconcile pharmaceutical profits and public health: fines, taxes, and pricing.

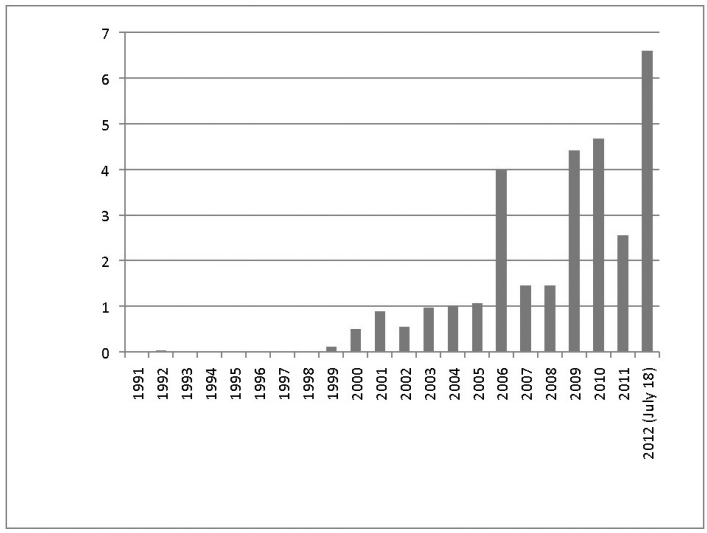
Increasing Fines for Misconduct

One reform seems self-evident: increase fines and penalties for illegal behavior in order to transform the financial incentives at work.

The importance of illegal practices can be observed in the mounting fines against drug companies in the last decade in the United States. Since 1991, drug companies have paid $30 billion in criminal fines in the United States. These penalties arise mostly from out-of-court settlements for Medicare fraud, unlawful promotion, kickbacks, monopoly practices, and the concealment of study findings. In rare cases, there were fines for poor manufacturing practices, environmental violations, financial violations, and illegal distribution. While Medicare fraud is by far the most com-

Figure 2

Financial Penalties against Pharmaceutical Companies in the United States ($billion), 1991-2012



Source: Public Citizen[33]

mon reason for such settlements, unlawful promotion incurred the largest fines[34] and seems to be the norm, at least for some categories of prescription drug. A case in point is atypical antipsychotics, one of the most prescribed drug categories: in 2007, Bristol Myers Squibb paid $515 million in fines for unlawful promotion, kickbacks, and Medicare fraud in connection with the drug Abilify; in 2009, Eli Lilly settled for $1.4 billion over charges of off-label promotion for Zyprexa, and Pfizer settled for $301 million on charges of off-label promotion and kickbacks for Geodon; in 2010, Astra-Zeneca settled for $520 million on charges of ghostwriting, off-label promotion, and kickbacks for Seroquel; and in 2012, Johnson and Johnson settled for $1.2 billion on charges of off-label promotion and concealing information about the adverse reactions to Risperdal. According to IMS Health data, these five drugs remain the five best-selling atypical antipsychotic drugs in the United States, accounting for more than 75 percent of sales in the $18.2-billion market for antipsychotics in 2011.[35]

Fines for drug companies have recently set record highs. In 2009, Pfizer paid what, at the time, was the largest criminal fine ever imposed in the United States ($2.3 billion) in an out-of-court settlement for the off-label promotion of Bextra and other drugs. GlaxoSmithKline surpassed this record in 2012 with a settlement for $3 billion after pleading guilty to charges of unlawful promotion and failure to report safety data for drugs such as Avandia, Paxil, and Wellbutrin.

One might suppose that these fines would serve as a deterrent against socially harmful practices. However, given the profits and revenues of these companies, such fines have little financial impact. During the period for which GlaxoSmithKline settled for $3 billion, sales for Avandia, Paxil, and Wellbutrin were $10 billion, $12 billion, and $6 billion, respectively.[36] The $30 billion paid for all financial penalties since 1991 is less than half the profits made in 2009 alone by just the 10 largest U.S. drug companies appearing in the *Fortune* 500.

As long as the level of fines is not significantly higher, it will remain profitable for drug companies to engage in such practices that undermine public health. Higher fines for illegal practices, however, can have unintended consequences. Fines for such illegal activity are normally covered through insurance premiums paid by the companies. Higher fines thus mean increased risk-premiums, which, in turn, create an important barrier to entry for newcomers in the sector. What could function as an obstacle to business as usual can become a differential advantage for the dominant pharmaceutical firms, since they are better equipped than smaller firms to face the increased regulatory burden and higher insurance premiums.[37] Increasing the level of fines might reduce the incidence of some illegal practices, but might also reduce competition and consolidate even further the power of the major pharmaceutical companies.

Another option is to complement financial penalties with criminal prosecution of corporate officers, directors, and managers. Few pharmaceutical executives have served any jail time for unlawful practices that have sometimes caused the death of thousands of patients.[38] In his remarkable book on corporate crime in the pharmaceutical sector, John Braithwaite reminds us, however, that corporations can still resort to defensive strategies such as having pre-selected executives ready to take the blame in case of criminal prosecution.[39] Although higher fines and criminal prosecutions should be used to reduce the financial incentives for many harmful corporate practices, authorities need to proceed with caution and understand the sector's competitive dynamics and its ability to adapt to such penalties.

Could a tax reduce those pharmaceutical company activities that generate profits at the social expense of unnecessary treatments, adverse effects, and treatments that cost more without doing more? Taxing only undesirable activities is difficult since, if we could easily identify them, they would not be taxed but eliminated. A possible solution is to tax all promotional activities directed towards health care professionals and use the revenues to promote more rational uses of medicines.

Using Taxes to Transform Financial Incentives

In 1920, Arthur Cecil Pigou developed the concept of "negative externalities" to explain that the social cost of an activity might not be covered by the private cost of the producer.[40] In order to compensate for such negative externalities, he suggested imposing taxes to cover the costs associated with the externality. The cost of the externality thus becomes included in the private cost of production and the state gains the resources necessary to compensate the social cost generated by the manufacturer. In economics, the idea of taxing negative externalities is now referred to as a "Pigouvian tax."[41]

Could a tax reduce those pharmaceutical company activities that generate profits at the social expense of unnecessary treatments, adverse effects, and treatments that cost more without doing more? Taxing only undesirable activities is difficult since, if we could easily identify them, they would not be taxed but eliminated. A possible solution is to tax all promotional activities directed towards health care professionals and use the revenues to promote more rational uses of medicines.

The idea of imposing a tax on promotional expenditures aimed at physicians is not far-fetched. In Italy, since 2005, the regulatory agency for prescription drugs, the Agenzia Italiana del Farmaco (AIFA), requires all international and national pharmaceutical companies operating in Italy to contribute five percent of their yearly expenditure for promotional activities targeting Italian health professionals to a national fund for independent research.[42] Promotional activities include advertisements, supporting materials, meetings, trade fairs, freebies and gifts, but not the salaries of sales representatives. In the first three years of the program, AIFA collected around $60 million per year, half of which was used to support independent research and independent drug information[43] and half to pay for expensive orphan drugs — those developed to treat rare diseases.[44] In the United States, a tax like that could reduce returns on promotional spending and create public funding for independent drug information; for example, by funding public clinical trials to determine which drug should be used as a first-line treatment for a specific condition or by funding academic detailing or non-commercial-based educational outreach to promote the rational use of medicines.

Some issues need to be taken into account before implementing such taxes. First, if the funding of programs for public research or academic detailing is determined by how much tax can be levied from pharmaceutical promotion towards physicians, then those programs can become dependent on the activity that creates negative externalities. The agencies managing the programs could end up calling for *more* corporate spending on drug promotion.[45] This problem can be resolved by disconnecting program funding from the amount of taxes obtained. In that case, however, we end up not with a tax to recoup the negative externality, but simply a tax to reduce the financial returns on promotion.

The second problem is that such a tax would suggest that all promotional activity aimed at physicians induces a social cost. In theory, pharmaceutical promotion can be useful to disseminate knowledge and make health care professionals aware of new treatments, in which case a tax would be counterproductive. However, a systematic review published in *PLoS Medicine* in 2010 showed that the existing literature offered no support for the idea that pharmaceutical promotion improves physicians' prescribing habits, while the bulk of the literature indicates that pharmaceutical promotion can undermine the rational use of medicines.[46] But then, if most promotion aimed at health care professionals undermines the goals of medicine, why not just prohibit promotion rather than taxing it? In spite of these problems, and because the outright elimination of pharmaceutical promotion might not be politically or legally feasible, a tax on promotion could help persuade companies to spend less on promotion and more on developing innovative therapeutics.

Pricing Based on Therapeutic Value

Where fines or taxes focus on the fine-tuning of financial incentives, transforming the rationale behind drug pricing can lead to systemic reform of the financial incentives in place.[47] Two approaches to transforming pharmaceutical pricing are being explored in different countries: reference-based pricing (RBP) and value-based pricing (VBP).[48]

The rationale behind RBP is that, since most new drugs do not offer any greater therapeutic benefits than others already on the market, therapeutically interchangeable drugs should be competing on price to gain market share. With RBP, a standard price or reimbursement level is set, often based on the lowest-priced drug in the class, and manufacturers may then price their drugs above or below this reference price as they see fit. If patients choose a more expensive drug than the reference price, then they pay for the difference out-of-pocket. RBP has been used in Canada (British Columbia), Germany, Netherlands, New Zealand, Norway, and Spain and by the Veterans Health Administration and employer-sponsored drug plans in the United States,[49] where RBP is often described as a "maximum allowable cost (MAC) program."[50] By

encouraging market competition between therapeutically interchangeable drugs, RBP significantly reduces prices, increases the use and adherence of targeted drugs, and promotes switching from expensive products to lower-cost alternatives.[51]

The advantage of RBP is that it establishes a reference price above which a budget constraint becomes central in determining which therapeutically equivalent product will be prescribed. Going back to the "dinner for three" metaphor, the third-party payer can now establish some pricing conditions to influence the physician's choice of therapeutically equivalent products to prescribe. The growing influence of the third-party payer also curbs the waiter's aggressive and sometimes unethical promotion of products. Pharmaceutical markets in which there is competition amongst therapeutically equivalent products will offer clear financial incentives for drug firms: new products offering a significant therapeutic advance will command a price premium, while new drugs therapeutically equivalent to existing ones will be put in competition with other products and earn much smaller revenues.

The limits of RBP, however, are also important. Therapeutic equivalence is not always obvious; for one thing, and we need to consider that different patients may react differently to "therapeutically equivalent" drugs especially in some therapeutic niches like anticancer drugs. RBP cannot apply to all therapeutic categories, but it certainly can be used for some popular categories such as proton pump inhibitors, statins, and calcium channel blockers. Another risk is that third-party payers might use RBP to reduce treatment costs to the detriment of patients' health; caution would be required because the impact of RBP on patients' health has not yet been carefully studied.[52]

A second type of pricing policy based on therapeutic value is called value-based pricing (VBP), whereby a price is negotiated on the basis of the new drug's therapeutic value, as determined through health technology assessment.[53] The idea is simple: getting value for money by paying for health outcomes. In order to do this, however, we need to measure therapeutic value and establish a price for each unit of incremental therapeutic value. Health technology assessment, by measuring the incremental therapeutic value of a drug through quality-adjusted life years (QALYs), can be used here as a way to bridge science and policy. Based on a sociopolitical decision reflecting societal values, authorities can fix the price they are ready to pay for each QALY (for example, $50,000 per QALY). Such a threshold is important, as it functions as an opportunity cost. If the cost of a health technology is more than $50,000 per QALY, then public health is better served by spending money on some other health technology for which the cost is at most $50,000 per QALY.

Many countries already use health technology assessment to decide whether or not to reimburse a drug.[54] VBP goes one step further by determining how much manufacturers will be paid for a patent-protected brand-name drug, based on the incremental therapeutic value it provides. In our "dinner for three" metaphor, VBP means that the third-party payer will let the physician prescribe whatever he wants, but will pay the waiter only according to that treatment's incremental utility for the patient over other existing treatments. The advantages of VBP are that it makes evidence-based medicine (rather than marketing-based medicine) central to the architecture of the pharmaceutical market, and it directly aligns financial incentives with improving health outcomes. The pharmaceutical market would be reconstructed so that the only way for drug companies to increase their profits would be to increase their contribution to health outcomes. In order to rebuild the pharmaceutical market on evidence-based medicine through health technology assessment, VBP requires institutional capacity to independently assess clinical evidence and even to conduct independent clinical studies to obtain the best available evidence. Such institutional capacity could help tackle corporate practices that create bias in medical research. However, since health technology assessment depends mostly on published medical literature, a greater reliance on health technology assessment might also provide greater incentives for firms to multiply practices to create bias in medical literature. In order to avoid this pitfall, institutional capacity for health technology assessment should rely not only on published medical literature, but also on unpublished data. Greater transparency of unpublished clinical data would significantly improve the quality of heath technology assessment.[55]

However, VBP has several limitations. The main problem is the use of QALYs as a metric for incremental therapeutic contribution. Measuring the number of "standardized" life years gained by a population by the introduction of a new health technology is no easy task. QALYs — based on weighted preferences between different states of health — are a very blunt standard. They may not capture well how individuals value certain aspects of health, especially as compared to other aspects of life: they do not take equity, patient autonomy, and fairness into account because they do not make distinction in gained life years by age or disease severity.[56] Another problem is that an orphan drug treating a rare disease might offer a fantastic medical breakthrough, but its contribution in QALYs

to the overall population would be slight. VBP should thus consider a system of exceptions for orphan drugs.

Another limit of VBP is that it can only be implemented at a national level and in countries in which the state acts as the major or only drug purchaser. It thus seems suitable for European countries with universal pharmacare systems, but would be much more difficult to implement in the fragmented drug coverage systems of the United States and Canada. Also, VBP can only realign financial incentives if enough countries adopt it in parallel. At present, only Sweden officially uses VBP,[57] and the United Kingdom has announced that it will implement VBP in 2014.[58] VBP remains in theory the best way to realign financial incentives with public health, but the success of its implementation on a large scale remains uncertain. As they say in England, "the proof is in the pudding," and the U.K. experience with VBP should be followed carefully.

Conclusion

Imposing higher fines on unlawful promotion, taxing promotional activities, and using RBP or VBP could help reduce unlawful promotion. Higher fines for ghostwriting and for concealing research results and greater institutional capacity for health technology assessment could help deter unethical scientific practices that create bias in medical research. Such reforms, however, will have limited impact unless there is also greater transparency in drug-company-sponsored clinical trials. More radical solutions include (a) an outright ban on pharmaceutical promotion deemed to be harmful to prescribing habits and (b) publicly funded and conducted clinical trials. However, such radical reforms are probably politically unrealistic, while fines, taxes, and pricing reform could go a long way towards transforming the financial incentives in the pharmaceutical sector and reducing its institutional corruption.

Acknowledgements

The author would like to thank Marc Rodwin for all his comments and for the preparation of this special issue on institutional corruption, as well as Jason Dolny for his editorial assistance. All remaining errors are the author's sole responsibility. This research has received funding from the Canadian Institutes for Health Research.

References

1. M.-A. Gagnon and J. Lexchin, "The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States," *PLoS Medicine* 5, no. 1 (2008): 0029-0033.
2. M. Montalban and M. E. Sakinç, "How Financialization Shapes Productive Models in the Pharmaceutical Industry: The Domination and Contradictions of the Blockbuster Productive Model," GREThA Working Paper, Université of Bordeaux (2011); M.-A. Gagnon, *The Nature of Capital in the Knowledge-Based Economy; The Case of the Global Pharmaceutical Industry*, Ph.D. Dissertation, York University (2009).
3. B. Alpert, "Roche's Revolution," *Barron's* 85, no. 14 (April 4, 2005): 20-22.
4. A blockbuster drug is normally defined as a drug with sales of more than $1 billion per year.
5. M. A. Steinman et al., "Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents," *Annals of Internal Medicine* 145, no. 4 (2006): 284-293; D. Evans, "Big Pharma's Crime Spree," *Bloomberg Special Report*, December 2009; G. I. Spielmans, "The Promotion of Olanzapine in Primary Care: An Examination of Internal Industry Documents," *Social Science and Medicine* 69, no. 1 (2009): 14-20.
6. M. A. Rodwin, *Conflicts of Interest and the Future of Medicine* (Oxford: Oxford University Press, 2011); Institute of Medicine, *Conflicts of Interest in Medical Research, Education, and Practice* (Washington, D.C.: National Academies Press, 2009).
7. B. Goldacre, *Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients* (Toronto: McClelland & Stewart, 2012); B. Mintzes et al., "Pharmaceutical Sales Representatives and Patient Safety: A Comparative Prospective Study of Information Quality in Canada, France and the United States," *Journal of General Internal Medicine* 28, no. 4 (April 2013): 1-8.
8. See Gagnon and Lexchin, *supra* note 1.
9. S. Sismondo, "Ghost Management: How Much of the Medical Literature Is Shaped behind the Scenes by the Pharmaceutical Industry?" *PLoS Med* 4, no. 9 (2007): 1429-1433; A. Matheson, "Corporate Science and the Husbandry of Scientific and Medical Knowledge by the Pharmaceutical Industry," *BioSocieties* 3, no. 4 (2008): 355-385; G. I. Spielmans and P. Parry, "From Evidence-Based Medicine to Marketing-Based Medicine: Evidence from Internal Industry Documents," *Bioethical Inquiry* 7, no. 1 (2010): 13-29; S. Sismondo, "Linking Research and Marketing: A Pharmaceutical Innovation," in V. Quirke and J. Slinn, eds., *Perspectives on 20th Century Pharmaceuticals* (New York: Peter Lang, 2010): at 241-256.
10. S. Sismondo, "Ghosts in the Machine: Publication Planning in the Medical Sciences," *Social Studies of Science* 39, no. 2 (2009): 171-198; J. R. Lacasse and J. Leo, "Ghostwriting at Elite Academic Medical Centers in the United States," *PLoS Med* 7, no. 2 (2010): 1-4; U.S. Senate Committee on Finance, *Ghostwriting in Medical Literature*,111th Cong., June 24, 2010; S. Sismondo and M. Doucet, "Publication Ethics and the Ghost Management of Medical Research," *Bioethics* 24, no. 6 (2010): 273-283.
11. L. Cosgrove et al., "Financial Ties between DSM-IV Panel Member and the Pharmaceutical Industry," *Psychotherapy and Psychosomatics* 75, no. 3 (2006): 154-160; M. Angell, "Drug Companies & Doctors: A Story of Corruption," *NY Review of Books* 56, no. 1 (2009); see Institute of Medicine, *supra* note 6.
12. D. A. Kessler et al., "Therapeutic-class Wars: Drug Promotion in a Competitive Marketplace," *New England Journal of Medicine* 331, no. 20 (1994): 1350-1353; J. La Puma and J. Seltzer, "Phase IV Market Steams Ahead," *CenterWatch* 9, no. 10 (2002): 1-13; M. Andersen, J. Kragstrup, and J. Sondergaard, "How Conducting a Clinical Trial Affects Physicians' Guidelines Adherence and Drug Preferences," *JAMA* 295, no. 23 (2006): 2759-2764.
13. D. Healy, *Let Them Eat Prozac* (New York: New York University Press, 2004); E. H. Turner et al., "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy," *New England Journal of Medicine* 358, no. 3 (2008): 252-260; B. Hart, A. Lundh, and L. Bero, "Effect of Reporting Bias on Meta-Analyses of Drug Trials: Reanalysis of Meta-Analyses," *BMJ* 344, no. 7838 (2012).
14. U.S. Senate Committee on Finance, *Staff Report on GlaxoSmithKline and the Diabetes drug Avandia*, 111th Cong., 2nd Session, January, 2010; D. Egilman and E. Ardolino, "The Pharmaceutical Industry, Disease Industry," in W. H. Wiist, ed., *The Bottom Line or Public Health* (New York: Oxford Uni-

versity Press, 2010): at 193-224; E. Favereau and Y. Philippin, "Servier: La technique de l'intimidation," *Libération*, December 23, 2010; Prescrire, "Des firmes s'attaquent à des chercheurs," *Prescrire* 31, no. 328 (2011).

15. S. Miller, "Corruption," in E. N. Zalta, ed., *The Stanford Encyclopedia of Philosophy* (spring 2011 ed.), *available at* <http://plato.stanford.edu/archives/spr2011/entries/corruption/> (last visited June 17, 2013); L. Lessig, *Republic, Lost: How Money Corrupts Congress – and a Plan to Stop It* (New York: Twelve, 2011): at 226-248.
16. See Egilman and Ardolino, *supra* note 14; M.-A. Gagnon, "Corporate Influence over Clinical Research: Considering the Alternatives," *Prescrire International* 21, no. 129 (2012): 191-194.
17. See Gagnon, *supra* note 2.
18. OECD, *Pharmaceutical Pricing Policies in a Global Market* (Paris: OECD, 2008); S. J. Morgan et al., *The Public Provision of Pharmaceuticals: A Synthesis of Policies in Ten Developed Countries*, Pharmaceutical Policy Research Collaboration, December 2012.
19. P. Gorry, M. Montalban, and A. Smith, "When Medical Science Meets Economics & Politics: The Institutionalization of Health Technology Assessment within the European Government of Pharmaceuticals," GEDI working paper, 2011.
20. E. Schoonveld, *The Price of Global Health* (Farnham: Gower Publishing Limited, 2011).
21. P. Drahos and J. Braithwaite, *Information Feudalism: Who Owns the Knowledge Economy* (London: Earthscan, 2002).
22. EFPIA, *The Pharmaceutical Industry in Figures* (EFPIA-Various years), *available at* <http://www.efpia.eu/documents/80/61/The-Pharmaceutical-Industry-in-figures-Edition-2013> (last visited June 26, 2013); E. David, T. Tramontin, and R. Zemmel, "Pharmaceutical R&D: The Road to Positive Returns," *Nature Reviews Drug Discovery* 8, no. 8 (2009): 609-610. For a discussion of the misalignment of incentives for research and development, see M. A. Rodwin, "Five Un-Easy Pieces to Pharmaceutical Policy Reform," *Journal of Law, Medicine & Ethics* 41, no. 3 (2013): 581-589.
23. Patented Medicines Price Review Board, *Annual Report 2011* (Ottawa : PMPRB, 2012); Prescrire, "L'année 2012 du medicament; Progrès en berne, mesures timides pour la protection des patients," *Prescrire* 33, no. 352 (February 2013): 134-137; D. Light and J. Lexchin, "Pharmaceutical Research and Development: What Do We Get for All That Money," *BMJ* 345, no. e4348 (August 2012): 22-28. Note that Light and Lexchin contend that there is no innovation crisis in terms of the number of new drugs arriving on the market, but that there is a real innovation crisis in terms of the therapeutic innovation that these new drugs represent. See also, D. W. Light, J. Lexchin, and J. Darrow, "Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs," *Journal of Law, Medicine & Ethics* 41, no. 3 (2013): 590-600.
24. G. Harris, "Federal Research Center to Help Develop Medicines," *New York Times*, January 22, 2011.
25. For more information on methods, see Gagnon, *supra* note 2.
26. A. Fretheim, "Back to Thiazide-Diuretics for Hypertension: Reflections after a Decade of Irrational Prescribing," *BMC Family Practice* 4, no. 19 (2003): 1-4; A. Pollack, "The Minimal Impact of a Big Hypertension Study," *New York Times*, November 27, 2008.
27. P. B. Jones et al., "Randomized Controlled Trial Effect on Quality of Life of Second- vs. First-Generation Antipsychotic Drugs in Schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1)," *Archives of General Psychiatry* 63, no. 10 (2006): 1079-1087; R. R. Girgis et al., "Clozapine v. Chlorpromazine in Treatment-Naïve, First-Episode Schizophrenia: 9-Year Outcomes of Randomised Clinical Trial," *British Journal of Psychiatry* 199, no. 4 (2011): 281-288.
28. J. Fournier et al., "Antidepressant Drug Effects and Depression Severity: A Patient-Level Meta-analysis," *JAMA* 303, no. 1 (2010): 47-53; I. Kirsch, *The Emperor's New Drugs: Exploding the Antidepressant Myth* (New York: Basic Books, 2010).
29. A. Fugh-Berman, "The Haunting of Medical Journals: How Ghostwriting Sold 'HRT,'" *PLoS Medicine* 7, no. 9 (2010): 1-11.
30. See Sismondo, *supra* note 9.
31. See Spielmans and Parry, *supra* note 9.
32. S. Norris et al., "Characteristics of Physicians Receiving Large Payments from Pharmaceutical Companies and the Accuracy of Their Disclosures in Publications: An Observational Study," *BMC Medical Ethics* 13, no. 24 (September 2012): 1-7; R. Pear, "U.S. to Force Drug Firms to Report Money Paid to Doctors," *New York Times*, January 16, 2012. For discussions of the limitations of transparency, and its potential benefits, see in this issue of *JLME* 41, no. 3 (2013): S. Sismondo, "Key Opinion Leaders and the Corruption of Medical Knowledge: What the Sunshine Act Will and Won't Cast Light On," 635-643; Y. Feldman, R. Gauthier and T. Schuller, "Curbing Misconduct in the Pharmaceutical Industry: Insights from Behavioral Ethics and the Behavioral Approach to Law," at 620-628; A. Brown, "Understanding Pharmaceutical Research Manipulation in the Context of Accounting Manipulation," at 611-619; L. Cosgrove and E. E. Wheerler, "Drug Firms, Codification of Diagnostic Categories & Bias in Clinical Guidelines," at 644-653.
33. S. Almashat and S. Wolfe, *Pharmaceutical Industry Criminal and Civil Penalties: An Update*, Report for Public Citizen, September 27, 2012.
34. See Almashat and Wolfe, *supra* note 33.
35. IMS Health data about sales for each drug are available the following website: <http://www.drugs.com/stats/top100/2011/sales> (last visited June 17, 2013). Data about total sales for antipsychotic drugs are available on the IMS Health website: <http://www.imshealth.com/portal/site/ims/menuitem.5ad1c081663fdf9b41d84b903208c22a/?vgnextoid=fbc65890d33ee210VgnVCM10000071812ca2RCRD&vgnextfmt=default> (last visited June 17, 2013).
36. See Goldacre *supra* note 7, at 346.
37. *The Economist*, "An Unhealthy Burden," June 30, 2007.
38. For example, in his testimony for the US Senate Finance Committee, David J. Graham, Associate Director for Science and Medicine in FDA's Office of Drug Safety, estimated that the drug Vioxx caused between 88,000 and 137,000 excess cases of heart attacks in the United States. Of these between 30% and 40% died. The drug was marketed by Merck between May 1999 and June 2004 in the United States. To promote the drug Merck organized a ghostwriting campaign involving around 96 scientific articles. Key ones omit mentioning the death of some patients during clinical trials. During a class action lawsuit against Vioxx in Australia in 2009, it was discovered that the company had created a fake medical journal for Merck – the *Australasian Journal of Joint and Bone Medicine*, published by Elsevier. Merck's internal e-mails, revealed during the class lawsuit, exposed that the company drew up a hit list of "rogue" researchers who needed to be "discredited" or "neutralized." Eight researchers at Stanford complained that they received threats from Merck after publishing unfavorable results. In the United States, the only charges against the company have been charges of unlawful promotion, for which the company agreed to pay $950 M in an out-of-court settlement. Between 1999 and 2004, sales amounted to $11 billion in the United States. See M.-A. Gagnon and S. Sismondo, "The Ghosts of Medical Research," *Genetic Engineering and Biotechnology News* 30, no. 10 (May 15, 2010); P. Loftus and B. Kendall, "Merck to Pay $950 Million in Vioxx Settlement," *Wall Street Journal*, November 23, 2011.
39. J. Braithwaite, *Corporate Crime in the Pharmaceutical Industry* (London: Routledge, 1984): at 308.
40. A. Pigou, *The Economics of Welfare* (New York: Macmillan, 1920). The clearest example of a negative externality is environmental pollution: a manufacturer can sell his product according to his private cost of production, but if the production process generates pollution (for example by spilling mercury in drinking water), this social cost is not included in the

private cost that the manufacturer has to pay. This external social cost, which is not included in the cost of production of the manufacturer, is a negative externality.

41. W. J. Baumol, "On Taxation and the Control of Externalities," *American Economic Review* 62, no. 3 (1972): 307-322.
42. AIFA Research and Development Working Group, "Feasibility and Challenges of Independent Research on Drugs: The Italian Medicines Agency (AIFA) Experience," *European Journal of Clinical Investigations* 40, no. 1 (2010): 69-86.
43. L. Moja et al., "Using *Clinical Evidence* in a National Continuing Medical Education Program in Italy," *PLoS Medicine* 4, no. 5 (2007): 799-802.
44. See AIFA Research and Development Working Group, *supra* note 42.
45. J. Lexchin, "Models for Financing the Regulation of Drug Promotion," *Globalization and Health* 8, no. 24 (July 2012): 1-7.
46. G. K. Spurling et al., "Information from Pharmaceutical Companies and the Quality, Quantity, and Cost of Physicians' Prescribing: A Systematic Review," *PLoS Medicine* 7, no. 10 (2010).
47. Current pricing incentives also encourage promotion of off-label prescribing. For a discussion of how to change reimbursement for drugs prescribed off label, see M. A. Rodwin, "Rooting Out Institutional Corruption to Manage Inappropriate Off-Label Drug Use," *Journal of Law, Medicine & Ethics* 41, no. 3 (2013): 654-664.
48. M. Drummond, B. Jonsson, F. Rutten, and T. Stargardt, "Reimbursement of Pharmaceuticals: Reference Pricing Versus Health Technology Assessment," *European Journal of Health Economics* 12, no. 3 (2011): 263-271.
49. J. L.-Y. Lee et al., "A Systematic Review of Reference Pricing: Implications for US Prescription Drug Spending," *American Journal of Managed Care* 18, no. 11 (November 2012): e429-e437.
50. V. H. Mabasa, "Effect of a Therapeutic Maximum Allowable Cost (MAC) Program on the Cost and Utilization of Proton Pump Inhibitors in an Employer-Sponsored Drug Plan in Canada," *Journal of Managed Care Pharmacy* 12, no. 5 (2006): 371-376.
51. See Lee et al., *supra* note 49.
52. S. Morgan, G. Hanley, and D. Greyson, "Comparison of Tiered Formularies and Reference Pricing Policies: A Systematic Review," *Open Medicine* 3, no. 3 (2009): 131-139.
53. D. Husereau, and C. G. Cameron, *Value-Based Pricing of Pharmaceuticals in Canada: Opportunities to Expand the Role of Health Technology Assessment?*, CHSRF Series of Reports on Cost Drivers and Health System Efficiency: Paper 5 (December 2011); K. Claxton et al., "Value Based Pricing for NHS Drugs: An Opportunity Not to Be Missed?" *BMJ* 336, no. 7638 (February 2008): 251-254.
54. See Gorry, Montalban, and Smith, *supra* note 19.
55. B. Wieseler, N. McGauran, M. F. Kerekes, and T. Kaiser, "Access to Regulatory Data from the European Medicines Agency: The Times They Are A-Changing," *Systematic Reviews* 1, no. 50 (October 2012): 1-4.
56. M. D. Smith, M. Drummond, and D. Brixner, "Moving the QALY Forward: Rationale for Change," *Value in Health* 12, Supp. 1 (March 2009): S1-S4; P. J. Neumann, "What's Next for QALYs?" *JAMA* 305, no. 17 (May 4, 2011): 1806-1807.
57. C. Sorenson, "Use of Comparative Effectiveness Research in Drug Coverage and Pricing Decisions: A Six Country Comparison," *Commonwealth Fund Publications* 1420, vol. 91 (July 2010); see Husereau and Cameron, *supra* note 53.
58. K. Claxton, M. Sculpher, and S. Carroll, *Value-Based Pricing for Pharmaceuticals: Its Role, Specification and Prospects in a Newly Devolved NHS*, Centre for Health Economics, University of York (2011).