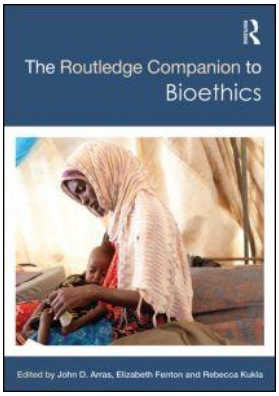

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INFLUENCE OF THE PHARMACEUTICAL INDUSTRY ON RESEARCH AND CLINICAL CARE

Howard Brody

Since the beginning of the twenty-first century, bioethicists have begun to pay serious attention to the influence that the pharmaceutical and medical-device industries exert over both medical research and patient care. Most authorities agree that the main ethical concern, if there is one, is conflict of interest. According to one viewpoint, the main goal of research is discovery of scientific truths for the benefit of the health of future patients, and the main goal of clinical care is the health benefit of the patient receiving attention. While it is possible that the drug and device industries can maximize their profits while also serving these goals, in too many cases there is a conflict between the goal of patient benefit and the goal of profit maximization. In such cases, influence exerted by industry may be deleterious to patients. To the extent that health care professionalism is defined as giving highest priority to the interests of patients, then industry influence becomes a threat to professionalism.

Alternative points of view dispute this portrayal. One such view is that the entrepreneurialism of industry provides a net patient benefit, through continued innovation in health care, so that any interference with the current system of relationships of physicians and medical scientists with industry would result in significant patient harm. Another related view is that the very idea of "conflict of interest," in this context, is vague and incoherent, and amounts to an *ad hominem* attack rather than a tool of ethical analysis.

Accordingly, a discussion of the bioethical significance of industry influence ought to answer these questions:

1. What are the available facts regarding the influence of industry over medical research and clinical care?
2. How is "conflict of interest" defined by those who believe that it serves a useful function in bioethical analysis?
3. What arguments are raised against the above view of "conflict of interest"?
4. If industry influence is detrimental to patient interests, with whom does the major responsibility lie?

Factual Concerns

Since about 2004, a number of book-length treatments expressing concern about the consequences of industry influence over medicine have appeared (Abramson 2004; Angell 2004; Kassirer 2005; Avorn 2004; Brody 2007; Weber 2006) though some books raising similar concerns were published much earlier (Silverman and Lee 1974; Braithwaite 1984). These works amass a considerable body of data showing that deleterious consequences arise from industry influence.

The degree of industry influence is substantial. One analysis claimed that in 2004 the total expenditures for marketing drugs to physicians and patients in the U.S. totaled $57 billion, many times the total budget for all medical schools and residency training programs (Gagnon and Lexchin 2008). Surveys showed that 94 percent of American practitioners reported some sort of contact with pharmaceutical marketers in 2004; by 2009 the number had dropped slightly, to 84 percent (Campbell et al. 2007, 2010).

Regarding clinical practice, a recent review systematically analyzed 58 published studies of the results of industry influence. The authors concluded that the majority of the studies showed that industry influence over practitioners was associated with a higher number of prescriptions, higher costs of prescriptions, and less rational prescribing. Virtually no studies found the opposite effects (Spurling et al. 2010).

A repeated finding in studies of physician attitudes is that while industry marketing appears to influence physician behavior, physicians themselves routinely deny that they are influenced in this manner (Orlowski and Wateska 1992). Physicians routinely report that they personally remain uninfluenced by industry marketing strategies, while admitting that their peers are readily swayed by the same types of marketing (Steinman et al. 2001).

Currently, a large majority of clinical studies related to pharmaceuticals are funded by industry. Numerous studies comparing commercially sponsored medical research with research funded by government agencies or non-profit foundations demonstrate a systematically greater likelihood that industry-funded research will favor the drug under study, by up to a four-fold difference (Lexchin et al. 2003). A particularly worrisome aspect of industry marketing is the practice of ghostwriting, in which medical writers hired by firms paid by a drug company write articles favorable to the company's drug, which are then submitted to widely read journals under the name of a respected academic physician, with no admission of the role of the hired writer (Leo et al. 2011). Ghostwriting assures that the commercial firm will exercise the maximum control over the content of the article, while creating the impression that the true author is an academic expert who is presumably unbiased. In the more extreme cases, what are actually infomercials touting a drug are disguised as scientific publications.

Influencing individual physicians to prescribe drugs for patients that may be inferior to alternative drugs, or to non-drug therapies such as diet and exercise, causes harm to individual patients. Exerting marketing control over the content of the medical literature, by contrast, potentially harms a much larger number of patients, because even physicians who conscientiously avoid industry marketing will be unable to tell the difference between scientifically valid results and industry-biased reporting. Increasingly, physicians rely on clinical practice guidelines written by expert panels to summarize scientific data in usable form. Studies have shown that many physicians sitting on these panels, as well as the organizations that produce the guidelines, receive substantial sums of money from the industry and so may be biased (Choudhry et al. 2002; Rose 2008).

One telling illustration of the degree to which the medical literature can be skewed through commercial influence is provided by a study of 12 different antidepressant drugs. The authors compared the published literature with the data supplied to the U.S. Food and Drug Administration (FDA) by the firms seeking approval to market their drugs (the latter obtained through the *Freedom of Information Act* as the FDA usually protects proprietary industry information from public release) (Turner et al. 2008). The authors found that about half of the clinical trials of these antidepressants failed to show that the drug was superior to placebo. The vast majority of these negative studies either were never published in medical journals, or were published with "spin" to represent the results as being positive. If a physician were to consult only the published literature, it would appear that scientific evidence strongly supported the efficacy of these medications. If the same physician had access to the complete and unbiased body of clinical trial data, it would seem a toss-up as to whether these drugs were effective or not.

An "Inverse Benefit Law" has been proposed to describe the relationship between pharmaceutical marketing and patient benefit (Brody and Light 2011). The "Law" (a heuristic device) claims that the ratio between benefit and harm of a drug turns more unfavorable the more vigorously the drug is marketed. To market a drug, a company must persuade physicians to lower the threshold at which the drug is prescribed, so that a larger percentage of the total patient population become candidates. As a rule, a drug is most beneficial when used among patients with the severest symptoms or the most severe physiological abnormality. An antihypertensive drug, for instance, will usually benefit someone whose baseline blood pressure is 180/110 much more than someone whose pressure is 150/95. Adverse reactions to drugs, by contrast, are randomly spread throughout the entire patient population. Therefore, lowering the prescribing threshold and exposing more patients with milder disease to the drug reduces population benefit and increases population harm.

In summary, the pharmaceutical industry spends considerable resources to influence both medical practice and medical science. The available evidence suggests that this influence has the potential to harm patient interests. Patients may be harmed when individual practitioners are influenced by contacts with drug sales representatives, for example, and prescribe less effective or less safe products. A more basic level of harm arises when the scientific evidence base is distorted by commercial influence over scientific research and publication. We assume that most of what is true of the pharmaceutical industry is also true of the medical device industry, but the latter industry has been less thoroughly studied.

Understanding Conflict of Interest

An often-quoted definition of "conflict of interest" in medicine is: "a set of conditions in which professional judgment concerning a primary interest (such as the patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)" (Thompson 1993: 573). Arthur Schafer (2004) has objected to this definition, noting that it trivializes the problem to see it as a conflict between competing *interests*. Physicians have an *interest* in receiving such gifts and emoluments from industry as free dinners, consulting and speaking fees, and research grants. By contrast, physicians have a *duty* to protect the patient's welfare and the integrity of research.

Ed Erde (1996) provides a more in-depth discussion of the definition of "conflict of interest." He notes first that the basic notion that conflict of interest addresses is *trust in*

a social role. This means that the often-cited distinction between "conflict of interest" and "apparent conflict of interest" is frequently spurious. The appearance of a conflict of interest can be just as destructive of trust as actual bad behavior.

Erde proceeds to suggest that two further distinctions *are* pertinent to describing a conflict. First, a physician may have a motive to act in a way that violates a professional duty; or she may merely have entered into certain social arrangements that increase a tendency or temptation to neglect that professional duty. The available evidence strongly suggests that an actual motive to neglect or violate professional duty is rare, and most conflicts in practice consist of entering into social arrangements that constitute serious temptations to neglect duties (such as relying on drug salespeople or detailers for information about new drugs rather than taking the time to consult less biased, evidence-based information sources).

A second distinction is between entering into the wrong sorts of arrangements without violating one's duty, and actually succumbing to the temptation and violating a duty. For example, one physician-scientist might accept company grants and consulting and speaker's fees while still remaining rigorous in conducting unbiased research. A different scientist might accept those fees and, as a result, allow his name to be attached to a ghostwritten article that inappropriately recommends a less beneficial or even harmful drug. The appropriate moral response in the first case is a warning, while in the second case it is moral condemnation. Again, the record suggests that the need for warning is a much more common occurrence in today's practice than outright bad moral behavior.

While Erde tries to describe a topology of conflict of interest rather than providing a single definition, it seems possible to employ his insights and to construct the following definition: *A conflict of interest exists in medicine when the following conditions have all been met:*

1. The physician has a duty to advocate for the interests of the patient (or public).
2. The physician is also subject to other interests—her own, or those of a third party.
3. The physician becomes a party to certain social arrangements.
4. Those arrangements, as viewed by a reasonable onlooker, would tempt a person of normal human psychology to neglect the patient's/public's interests in favor of the physician's (or third party's).

(Brody 2011)

This definition makes it clear that to allege a conflict of interest is not to accuse a physician of actually violating duties to patients. Rather, such an allegation points out a situation in which public trust in medicine could be weakened, through the reasonable interpretation that the physician would be strongly tempted to neglect duties to patients in that situation.

The next ethical question is whether a conflict of interest, having been identified, can best be handled by management or avoidance. Many recent guidelines promulgated by medical institutions speak predominantly of "managing" conflicts of interest, assuming that they cannot be eliminated or else that it would be undesirable to do so. A case example where management seems the appropriate strategy might be a research trial involving a novel device that shows great therapeutic promise. One particular surgeon has invented this device and has invested in a biotechnology firm that has agreed to develop the device. No other physician currently has enough experience with this device to design and administer a clinical trial. To allow this physician to serve as the principal investigator in a clinical trial of this device, while appointing a

special oversight committee to review all aspects of the trial design and conduct to be sure that the physician's financial interests in the device do not affect scientific integrity, might be the best way to handle this particular situation.

In other situations, however, the better approach might be to prohibit conflicts of interest and to demand that academic physicians divest themselves of conflicted financial ties to industry. Many commentators have characterized the "management" strategy as a too-facile acceptance of the status quo, and have called for a divestment strategy as superior in most cases (Schafer 2004; Kassirer 2005; Brody 2007). While a physician cannot be accused of violating duties to patients merely because a conflict of interest exists, a physician can be held ethically accountable for entering into social arrangements of the sort where neglect of patient duties becomes much more likely. This is especially so when the arrangements are not necessary for the conduct of clinical care or scientific research. No physician *needs* to visit regularly with drug detailers or accept free dinners from them in order to provide quality patient care. No investigator *needs* to accept speaker or consulting fees from a drug or device company in order to do research.

For many years such arrangements were accepted as part of the medical landscape and shielded from criticism. More recently, ethical concern has mounted over these practices and calls have increased for their prohibition (Brennan et al. 2006; Lo and Field 2009). One sign of the effectiveness of this ethical criticism is a step taken by the Pharmaceutical Research and Manufacturers of America (PhRMA), the national organization representing brand-name drug firms. In January 2009, PhRMA voluntarily inaugurated a new set of guidelines that eliminated many common marketing practices—perhaps most notably, pens and other "reminder items" emblazoned with the names of drugs. These guidelines were voluntary for industry and skeptical questions were raised as to their actual impact (PhRMA 2008). The point, however, is that the climate of public perception had changed sufficiently so that PhRMA apparently felt that previous marketing practices were unsustainable, and it was necessary to create at least the appearance of reform.

Conflict of Interest: Objections

The increased scrutiny of pharmaceutical marketing practices appears to represent a widely held ethical view, but a small but vocal group has raised some objections. This group of critics includes members of the Association of Clinical Researchers and Investigators, who appear especially concerned to advocate for free-market solutions in health care. One objection focuses especially on the concept of "conflict of interest."

Philosopher Lance Stell objects to current usage of "conflict of interest" as an epithet that amounts to an illogical *ad hominem* attack rather than a substantive mode of ethical inquiry (Stell 2009). He argues, first, that conflicts of interest are ubiquitous in medicine, as evidenced by the long history of fee-for-service payment (in which physicians are tempted to do extra, unnecessary procedures in order to maximize income). Fiduciaries, he states, are generally conflicted in multiple ways; it is simply unrealistic to imagine that one set of conflicts, financial ties to drug manufacturers, are uniquely incapacitating of one's ability to adhere to one's duties to patients.

Stell next notes the subjective elements of definitions like Erde's, "reasonable onlooker," "tempt a person of normal human psychology," etc. For a term to be of use in ethical inquiry, he suggests, there ought to be a reasonably agreed-upon, objective threshold for its application. There is no such agreed-upon standard for conflict of interest.

Hence this term can serve only as a kind of name-calling. Conflict-of-interest guidelines, Stell asserts, violate the industry's rights to free commercial speech, and potentially deny physicians useful information and resources that can benefit patients.

Stell's objections are open to several rebuttals. If, as Erde claims, the basic concept underlying conflict of interest is trust in a social role, then it is not surprising that the concept includes an irreducible element of subjectivity, since it is a subjective judgment when trust has been violated and how severely. Stell also appears to dispute the evidence summarized in an earlier section, and tends to assume that financial relationships will probably lead only to beneficial exchanges of information between medicine and industry. Finally, he lumps financial conflicts of interest with all other sources of bias that afflict medical science and practice. While it is indeed unrealistic to imagine one could eliminate all those sources of bias, financial conflicts of interest are generally unnecessary for medical practice and research and could in theory at least be eliminated. In addition, many other sources of bias, such as the desire of scientists to confirm their favored hypotheses, are obvious to the scientific reader. By contrast, financial conflicts of interest would remain hidden unless specific disclosure policies are adopted. Sander Greenland, an epidemiologist, has looked at different sources of investigator bias from a biostatistician's standpoint and argues that the rational reader, concerned to know the likelihood that the conclusions of a given study are true, would wish to be informed about financial conflicts of interest as a distinct, important category (Greenland 2009).

Law professor Richard Epstein (2007) agrees with Stell that conflicts of interest are ubiquitous, so that it is arbitrary to single out financial or gift ties between physicians and drug/device companies as particularly problematic. He adds the further concern that the cost of regulating or policing conflicts of interest would be greater than the cost of a laissez-faire approach. Citing the adage, "Who guards the guardians?" he argues that any oversight system would do little more than introduce an additional layer of further conflicts of interest, leading to an infinite regress. Epstein ignores two logical implications of his position, however: First, that all attempted regulation of commercial transactions is vain; and second, that there is no effective possibility of professional self-regulation (an odd position for a law professor to adopt). The most effective rebuttal to Epstein's claims would be a reasonable set of proposals for regulating financial conflicts of interest in medicine. I will discuss some such proposals briefly below.

Harmful Effects of Influence: Objections

Presumably, the whole reason to try to identify and deal with conflicts of interest in this area is because of the dangers of harm to patient interests. While a great many works have documented a large number of examples of possible harms, a few have objected that these harms are in fact illusory.

Stell has joined forces with physician-investigator Thomas Stossel to argue that patients are best served by a robust system of financial ties between physicians and medical scientists with industry (Stell and Stossel 2011). As in other areas of life, financial incentives work to stimulate the maximum effort toward innovation, leading to improved cures. If "professional" efforts to rein in conflicts of interest were successful, innovation would be severely curtailed, leading to significant harm to patients in the future. Stossel argues further that the examples cited by critics of the deleterious consequences of industry influence over science and practice are unrepresentative and constitute unreliable anecdotal evidence. Presumably, critics of the drug industry object

to the publication of biased research reports because these make it difficult for physicians to practice evidence-based medicine. If the critics were consistent, then they would require the same high evidence-based standards before accusing the industry of exerting a deleterious influence over medical practice and research. This evidentiary standard, argues Stossel, is one from which critics have fallen short (Stossel 2007).

It is worth asking what would count as evidence for a deleterious influence that would meet the high standards Stossel recommends. Focus for now on medical practice only. It is often held that the gold standard for evidence of a causal connection is a randomized controlled trial. Meeting Stossel's standards of evidence would require that medical students, on matriculation, be randomly assigned to two groups. One group would be encouraged to have maximum contact with drug industry representatives and marketing, while the other would be strictly forbidden to have such contact. After perhaps 10 years, the health of the patients cared for by the two groups of physicians would be measured and compared. Only if the health of the patients of the second group of physicians was significantly better than that of the first group would the conclusion be allowed that industry marketing exerted a negative influence over medical practice.

The point about this hypothetical randomized trial is its utter impracticality. Since no such definitive trial is ever going to be conducted, a better question is the degree to which the partial, incomplete evidence assembled to date is sufficiently suggestive to yield policy recommendations. As noted, the review by Spurling and colleagues (2010) suggests a substantial unanimity in the direction of findings among the available research studies, all tending in the direction that the influence of industry contact among practitioners yields potentially deleterious effects. Since Stell and Stossel apparently remain unpersuaded by the evidence amassed by investigators such as Spurling et al., one has to question whether, by demanding "better quality" evidence, they are deliberately setting the bar so high as to be practically unreachable.

Defenders of close financial relationships between medicine and the pharmaceutical industry commonly cite a series of research studies by the economist Frank Lichtenberg (2001). Lichtenberg has searched large databases and concluded that there is a close association between greater life expectancy and higher expenditures for newer, brand-name drugs. The implication is that physicians who have closer contacts with industry marketers are more likely to prescribe such drugs (a finding with which Spurling et al. (2010) would concur). Since the result of prescribing more of these drugs is patients who live longer, whatever influence the industry exerts over physicians is beneficial. There are, however, several problems with the methods used by Lichtenberg (Law and Grepin 2010). To mention just two concerns related to biological implausibility, Lichtenberg's methodology appears to assume that a new brand-name antihistamine for allergies is as likely to extend patients' lives as a drug to prevent heart attacks, and that a drug that is preventive in nature, and so might at best reduce mortality after a 5–10-year lag period, can demonstrate reduced mortality in the first year after it is prescribed. Moreover, considerable evidence exists to show that a number of widely prescribed, newer, brand-name drugs are no better than older generics, or else have little beneficial effect on health outcomes (Leucht et al. 2009; Gale 2001; Roberts 2012).

Assigning Ethical Responsibility

Even if some of the objections defending closer ties between medicine and industry appear to be plausible if not conclusive, one might accept for purposes of argument that the case

has been made that conflicts of interest at the interface between medicine and the drug and device industries threaten patients' health. Assuming this to be the case, the final question is where ethical responsibility lies for taking effective remedial action.

I will address three arguments:

1. Fault lies primarily with the industry, and the correct action is tighter government regulation.
2. Fault lies at least in part with industry, and a part of the solution lies in more ethical business practices.
3. Fault lies to a large degree within the medical profession, and solutions require a heightened sense of and dedication to high professional standards of behavior.

Assigning primary responsibility to industry may seem warranted in light of the frequency with which industry behavior crosses the line from the ethically questionable to the illegal. Sociologist John Braithwaite alleged as long ago as 1984 that the global pharmaceutical industry was disproportionately engaged in corporate crime (Braithwaite 1984). More recently, drug firms have prominently led the list of U.S. corporations settling with the Federal government over allegations of illegal acts, in some cases paying fines in excess of $1 billion (Feeley and Fisk 2012). The fact that several of these companies are repeat offenders suggests that skating as close as possible to legal limits is seen by industry as a routine business practice. Sen. Charles Grassley (R-IA) has been a consistent critic of the industry and has led investigations into its misdeeds (Wadman 2009). The *Federal Sunshine Act*, which became law as a part of the *Affordable Care Act* of 2010, is a significant legislative step to require public access to information about payments made by drug firms to physicians (Anonymous 2012).

Leonard Weber suggested a somewhat different approach in his study of the business ethics of the pharmaceutical industry (Weber 2006). Weber argued that the current behavior of the industry, which threatens medical professionalism through promoting deleterious conflicts of interest, falls distinctly short of the ethical responsibility of these firms as good corporate citizens. On the assumption that ethical business behavior is, in the long run, in the interests of the industry as well as society generally, Weber proceeds to argue for reforms that can be brought about within the drug industry.

These two approaches are not necessarily in competition. In the present climate, a single drug or device firm that chooses to act more ethically might lose market share when competitors are not similarly constrained. Appropriate government regulation might level the playing field and thereby encourage enhanced attention to ethics among the firms.

Other authors have focused more on the responsibility of the medical profession itself to police the interface with the pharmaceutical and device industries (Kassirer 2005; Brody 2007). On this line of argument, when companies ignore ethics, patient well-being, and sound science in order to maximize profit, they are simply doing what they are expected to do in a capitalist society. On completion of their business degrees, corporate executives swore no oath to protect patients and adhere to the integrity of medical practice, but physicians did. The primary obligation, therefore, lies with physicians and scientists to refuse to collaborate with industry in ways that create serious conflicts of interest. It is important to note, for example, that all drug detailers would be out of a job tomorrow if all physicians refused to see them; and drug company speakers' bureaus would largely cease to exist if all physicians declined to participate. That physicians and

medical scientists so frequently accept the gifts and payments offered by industry reflects much more on their own professionalism than on industry ethics.

The marketing of medical drugs and devices is a complex activity. Kalman Applbaum, an anthropologist, analyzes industry behavior in terms of "controlling the channels," by which he means that the company seeks to manage every aspect of a drug from discovery through manufacture through its eventual prescription to patients (Applbaum 2009). It would seem to follow that a program to achieve ethically optimal discovery and use of drugs and devices would need to be similarly complex and multi-faceted. Appropriate government regulations, an enhanced sense of business ethics, and greater attention to professional responsibilities would all seem to be vital parts of an overall program of reform (Brody 2007).

Those like Stell (2009) and Epstein (2007) who dismiss concerns about conflicts of interest allege that any set of regulations addressing this pseudo-problem would simply add unnecessary and ineffective layers of bureaucracy. Indeed this argument might have merit if close financial ties between medical scientists and the pharmaceutical industry were absolutely essential for desired innovation to occur; intrusive efforts to police the financial ties might well then detract from an environment fully conducive to innovation and discovery. But as Schafer (2004) pointed out, all arguments in favor of close connections between the drug industry and the medical profession call for the ready exchange *of information* so as to facilitate innovation. There is, Schafer notes, no reason besides habit and greed to imagine that this exchange of information need be accompanied in all cases by an exchange of *money*. The ideal direction for reforms, both intraprofessional and governmentally imposed, would therefore be to assure that information flows freely but without the corrupting influence of gifts of value. In the realm of medical practice, for example, there already exist a number of sources of commercially unbiased information about pharmaceuticals; the question is whether practitioners will develop the professional integrity to seek out those sources and refuse to see industry sales representatives as their preferred source of information (and free lunches and dinners) (Evans et al. 2013). By contrast, removing inappropriate financial incentives in research will probably require more than professional action alone; many believe that ultimately, the financing of clinical trials needs to be removed from industry and placed in the hands of a neutral government agency such as the National Institutes of Health (Avorn 2004; Brody 2007).

If intraprofessional reforms have an important role to play in governing conflicts of interest, then the education of future physicians and other professionals becomes paramount. It is encouraging in this regard that some of the earliest calls for substantial reforms came from leaders of academic medical centers, and many such centers have made great progress in removing sources of industry influence (Brennan et al. 2006).

While I have assumed that medical devices raise most of the same ethical issues as drugs, and require many of the same measures to address conflicts of interest, there are a few important differences. One is the greater importance of hands-on contact with the sales representative in the case of devices. Devices often require practical demonstration before physicians can use them properly and many device representatives are highly trained biomedical engineers. While the need for this hands-on contact can easily be exploited by device companies, it cannot be easily eliminated. Regulations for device marketing will of necessity be different from those for drugs.

Related Topics

Chapter 11, "Intellectual Property in the Biomedical Sciences," Justin B. Biddle
Chapter 12, "Bias, Misconduct, and Integrity in Scientific Research," David B. Resnik

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