

COMMENTARY

Conflict of interest or ideological divide: the need for ongoing collaboration between physicians and industry

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ABSTRACT

Continued collaboration between the health profession and industry is essential for future innovation and for fighting disease and illness well into the 21st century. Evidence that suggests conflicts of interest have a negative effect on patient care or the total cost of health care is lacking. Many arguments put forth to address this issue include strictly limiting or severing ties with industry. Research takes place in university, government, and pharmaceutical laboratories, but

only industry translates research into drug therapy. While both parties have a shared goal of optimizing health outcomes, industry critics conveniently invoke 'conflict of interest' to express their opinion about the need to more strictly regulate physician/industry interactions. Retreat from industry by academic institutions and working in isolation are simply not strategic options and other points of view must be expressed to help avoid the 'triumph of emotion over fact'.

Introduction

The topic of whether interactions between individual physicians and/or institutions and industry can lead to physician/institutional bias continues to generate great interest and debate¹⁻¹⁶. Many of the physician and academic medical center (AMC) perspectives arise from the belief that conflicts of interest are pervasive and that the current guidance provided by the interested bodies fails to protect the best interests of patients and the integrity of physician decision-making^{1,3,7,8,9,12}. It cannot be denied that in recent years several instances of industry misconduct have come to light, e.g., TAP/Lupron and Pfizer/Neurontin. While these cases no doubt fueled the current debate on collaboration between industry and physicians, unfortunately, such instances of unethical or criminal behavior are not limited to the pharmaceutical industry, e.g., Enron, Worldcom, Tyco.

Most recently, a special communication in the January 2006 issue of *J Am Med Assoc*, by Brennan

and colleagues, makes a strong recommendation for AMCs to take a leadership role in severing vital ties with industry². The authors claim that current measures to impose regulation on interactions between health care professionals and the pharmaceutical, biotechnology, and device industries are inadequate. The Pharmaceutical Research and Manufacturers of America (PhRMA), the Accreditation Council for Continuing Medical Education (ACCME), and the Office of the Inspector General (OIG) have provided recent guidance on this matter, and it is far too early to assert these measures are inadequate. Brennan and colleagues call for more stringent regulations that eliminate activities that could be regarded as a conflict of interest. Specifically, they suggest that AMCs: (1) eliminate all gifts to physicians, both practice- and non practice-related (zero dollar limit); (2) eliminate all pharmaceutical sampling, replacing it with a voucher system that would benefit low-income patients; (3) remove any health care providers with financial ties

to industry from formulary committees; (4) prohibit pharmaceutical manufacturers from providing financial support to any ACCME-accredited programs and establish central repositories at AMCs for manufacturer contributions to be disbursed to accredited CME providers; (5) divert funds for faculty or fellows' travel expenses to a central office at AMCs; (6) prohibit faculty members at AMCs from serving on speakers' bureaus for pharmaceutical or device manufacturers; and (7) increase the transparency of consulting and research funding².

Brennan and colleagues base their recommendations on a systematic review of the literature by Wazana that 'found that an overwhelming majority of interactions (with industry) had negative results on clinical care'². This statement is both incorrect and misleading. The stated objective of Wazana's study was to explore the relationship between physicians and the pharmaceutical industry and its representatives and examine the impact of this relationship on physicians' knowledge, attitudes, and behavior³. While Wazana's study claims that interaction with industry resulted in non-rational prescribing and decreased the use of generic agents, she presents no direct evidence that physician/industry interactions have a negative impact on patient outcomes.

In her study, Wazana searched MEDLINE and a database of 400 articles gathered by the Medical Lobby for Appropriate Marketing, identifying 538 studies that provided data on at least one of the study questions. A total of 29 were deemed relevant and included in the final analysis³. More importantly, no study in the analysis used patient outcome measures. Ironically, Blumenthal, a co-author of the Brennan paper, previously and correctly noted that Dr. Wazana found no studies that directly measured the effects of relationships between physicians and drug companies on patients' outcomes or on the aggregate cost of health care³. Wazana did conclude that there was evidence that physician–industry interactions appeared to affect prescribing habits and professional behavior, recommending that these interactions be further addressed at the policy level and through education³. It should be noted that Wazana's bias is distinctly anti-industry and yet, despite extensive data mining, she could not provide evidence of a negative impact on patient outcomes. Separately, Stossel reported in the *New Engl J Med* that no data exist showing that commercial involvement in academic research increases the rate of real or apparent adverse events as compared with research without that involvement¹.

Recent reports have called attention to several industry and government practices and review of these is timely and warranted.

Weighing the evidence

Sampling and the role of the pharmaceutical representative

Wazana reported that accepting samples was associated with awareness, preference, rapid prescription of a new drug and a positive attitude toward the pharmaceutical representative³. Many would argue that this service, as well as educational activities and industry support of guideline formulation and dissemination, complements the efforts of health care professionals and brings value to patients and medicine. In addition, it is important to note that not all promotion is of 'new' drugs. Many companies continue to promote older drugs that may be less expensive than newer entries to the market but offer similar or superior benefits.

Formularies

According to Wazana, physician interaction with the pharmaceutical industry increases the likelihood of a related formulary request (OR 3.4; 95% CI, 1.8–6.6) but the merit of the request was not related to interactions with the pharmaceutical industry³. Thus, it would appear that the multi-disciplinary nature of many formulary committees, and the rigorous review and drug selection processes they follow, ensures that they are not negatively influenced by industry.

FDA Advisory Committees

A recent, cross-sectional study using agendas and transcripts from all FDA Drug Advisory Committee meetings from 2001 to 2004 was completed. Predictor variables (index conflict, competitor conflict, any conflict) and outcome variables (vote favoring or not favoring the index product) were analyzed according to the Mantel–Haenszel method to provide a single weighted relative risk. The results of the analysis did not show a statistically significant relationship between predictor variables and outcome variables¹⁷.

The importance of sustaining and strengthening physician–industry interactions

Interactions between academic medical centers and industry have increased substantially during the past two decades, fueling medical innovations and new types of research collaborations. Consumers benefit with new medical devices and drugs that improve health care. Physicians and scientists gain by having access to resources, technology, and ideas that would

otherwise be unavailable or in limited supply. In fact, some of the greatest and earliest milestones in medicine have been realized through direct collaboration between academic physicians and industry. For example, in 1921, Frederick Banting, a medical doctor, and Charles Best, a young student, were able to extract insulin from the pancreas of a dog. When the extracted insulin was injected into a diabetic dog, Banting and Best noted that it successfully regulated the dog's sugar metabolism. Following their discovery, Banting and Best partnered with Eli Lilly & Co. in an effort to produce large quantities of insulin. By 1923, Eli Lilly & Co. introduced Iletin as the first commercially available insulin in the US. Frederick Banting was later knighted for his research and shared the 1923 Nobel Prize with his mentor, John Macleod¹⁸.

In a similar collaboration, in 1928, Scottish scientist Alexander Fleming discovered a substance that killed staphylococcal bacteria in a Petri dish; he later named this substance penicillin. Fleming's interest in penicillin waned over the next few years, and it was not until World War II that the true medicinal effects of his discovery were realized. The US War Production Board ordered the mass production of penicillin for the treatment of deadly infections in US troops. Penicillin became the world's first antibiotic, initially produced by 21 leading American manufacturers, including Lederle, Merck, Pfizer, Squibb, Eli Lilly, and Abbott Laboratories^{18,19}.

An estimated 371 000 new cases of invasive cervical cancer are diagnosed world wide each year, representing nearly 10% of all cancers in women. In frequency, it is the seventh cancer site overall and third among women, after breast and colorectal cancer²⁰. The clinical success and recent FDA approval of a cervical cancer vaccine is another striking example of intensive collaboration among academic institutions, government agencies, and the pharmaceutical industry. The science and technology behind the human papillomavirus vaccine arose from the work of dozens of researchers from the National Cancer Institute, Georgetown University, the University of Rochester, and other academic institutions. The vaccine was then licensed for commercial production to both Merck and GlaxoSmithKline by the National Cancer Institute. Successful clinical trials of the vaccine were supported by the two companies and led by researchers at leading academic institutions in the US and Europe. Merck's version of the vaccine, Gardasil, was approved by the FDA in June 2006 and will be available by the end of 2006; GSK's Cervarix is successfully finishing Phase III trials. It is this model of academic and industry collaboration that has produced scientific breakthroughs and highly effective therapies in far too great a number to detail here.

Why an AMC-centric approach is not sufficient or appropriate

When considering Brennan and colleagues' proposal, it is important to recognize the status and capability of many AMCs. Blumenthal pointed out that AMCs have certain disadvantages. For a start, they generally lack the faculty and clinical settings necessary to train primary care practitioners or the investigators required for outcomes and quality of care research²¹. The tremendous medical capability of AMCs notwithstanding, they are often plagued by entrenched bureaucracies and rivalries that may well impede their ability to disburse grants from a central fund. This reality is not likely to give industry, or any major philanthropic source, the confidence necessary to hand over hundreds of millions of dollars with no certainty of its destination or known effect of its ultimate use.

Pardes points out that funding of teaching hospitals and medical schools are inadequate²². With this in mind, it is not surprising that the recommendations made by Brennan and colleagues have vast dollars flowing into AMC repositories while stopping short of suggesting that AMCs walk away from additional consulting and research dollars.

The idea of giving funds to central repositories at AMCs raises an important issue. First, it directly calls into question the capability and credibility of the 737 accredited CME providers in the United States. The ACCME is governed by seven member organizations: the American Board of Medical Specialties, the American Hospital Association, the American Medical Association, the Association for Hospital Medical Education, the Association of American Medical Colleges, the Council of Medical Specialty Societies, and the Federation of State Medical Boards of the US, Inc. ACCME guidelines and essentials clearly mandate how accredited providers must operate. Nevertheless, companies should be able to specify that CME funds are used for topics in areas of therapeutic interest. In recommending the central repository approach, Brennan and colleagues fail to explain how prohibiting industry from providing direct financial support for accredited programs and instead creating layers of bureaucracy responsible for disbursement of funds will result in more effective CME programs. In fact, the concept of a central repository at AMCs is like taxation without industry representation.

Some industry critics have true concerns about the role of industry in producing and marketing drugs and the extremely relevant position they have earned through their commitment to science and drug development. However, rather than offering

constructive reforms that would make the interactions more efficient and credible, the critics veil their concerns and difference of opinion in a conflict of interest cloak. Perhaps, most important, critics of perceived conflicts of interest should encourage the medical profession to look at its own conduct and not place responsibility for these perceived problems solely on the pharmaceutical industry. A similar approach was suggested by Moses and colleagues, who called for AMCs to hold individual faculty members accountable for their relationships with industry²³.

Industry on stage – major changes underway

While the pharmaceutical industry has been on center stage for years, several recent developments have precipitated new laws and guidelines that address how industry must interact with health care professionals and it is simply too early to determine whether these important steps, outlined in Table 1, are working.

PhRMA guidelines

In April 2002, the Executive Committee of the Pharmaceutical Research and Manufacturers of America (PhRMA) unanimously adopted a new marketing code to govern the pharmaceutical industry's relationships with physicians and other health care professionals²⁴. The voluntary code took effect on July 1, 2002. The proactive move addressed mounting criticism of some sales and marketing practices and industry interaction with health care professionals. In essence, the code emphasizes that interactions between sales representatives and health care professionals should benefit patients and enhance medical practice, explicitly

saying that all interactions should focus on providing scientific and educational information about products and supporting medical research and education²⁴.

OIG guidance

The Office of the Inspector General (OIG) of the US Department of Health & Human Services (HHS) issued the Compliance Program Guidance for Pharmaceutical Manufacturers in April of 2003 to prevent and reduce fraud in federal health care programs²⁵.

The OIG guidance directly addresses many of the concerns raised by Brennan *et al*. The overarching recommendation by the OIG is for manufacturers to develop a 'clear statement of detailed and substantive policies and procedures at the core of a compliance program, including a statement of principles and code of conduct'²⁵.

With respect to relationships with formulary committee members, the guidance recognizes the temptation for unscrupulous manufacturers to influence decisions and cautions against direct or indirect remuneration to affect these decisions.

The OIG guidance reinforces the value of CME, explicitly recognizing that pharmaceutical manufacturers often fund continuing medical education programs. The OIG suggested that manufacturers should separate their grant making functions from sales and marketing functions²⁵. This guidance, which carries massive organizational design and implementation cost burdens, has been widely adopted by industry.

Regarding drug samples, the OIG recognizes that the provision of samples is 'a widespread industry practice that can benefit patients ... manufacturers should closely follow the Prescription Drug Marketing Act of 1987, which governs the distribution of drug samples and forbids their sale'²⁵.

Table 1. Industry codes of conduct

Issuing body	Title	Key dates	Basis of compliance
Pharmaceutical Research and Manufacturers of America (PhRMA)	Code on interactions with health care professionals	Issued April 2002, effective July 2002	Voluntary for PhRMA members, but viewed by HHS as the 'starting point' for compliance with anti-kickback statutes
Office of the Inspector General (OIG) of the Dept of Health & Human Services (HHS)	Compliance program guidance for pharmaceutical manufacturers	April 2003, effective on date of publication	Addresses three areas of pharmaceutical industry practice: sampling, kickbacks to physicians, and pricing information, all with the intent to eliminate untoward pharmaceutical influence over prescribers
Accreditation Council of Continuing Medical Education (ACCME)	Standards for commercial support	Issued April 2004 adopted September 2004, effective for new CME May 2005, effective for all CME November 2006	Required for accredited CME programs

ACCME policy revisions

The revised Standards for Commercial Support were adopted by the ACCME board of directors on April 1, 2004²⁶. By November 2006, through a phased approach, 'substantial compliance' will be required in order to receive provisional accreditation or re-accreditation. The primary objective of the ACCME's revised standards is to 'avoid commercial bias' in educational activities by ensuring that presentations are balanced and based on objective, evidence-based science. Specifically, the Standards require that the following decisions be made by the accredited CME provider in a way that is free of the control of a commercial interest²⁶: identification of commercial needs, determination of medical objectives, selection and presentation of content, selection of all persons and organizations that will be in a position to control the content of the CME, selection of educational methods, and evaluation of the activity.

The road ahead

Organized medicine and the pharmaceutical industry are among the two most capable and potent health care stakeholders in the world – both are committed to pushing the frontier of science and medicine to enhance health and extend life. Collaborative work among medical professionals, pharmaceutical, biotechnology, and device companies has made a profound impact on reducing the burden of disease and enhancing quality of life. Industry deserves a meaningful place at the table as well as respect for their commitment as dedicated scientists and business professionals.

The true extent (depth and breadth) and negative consequences (if any) of interactions between industry and health care professionals are unknown. Scandals are inevitable and no rules will prevent them from occurring⁴ nor can integrity be mass imposed by public policy. There is nothing inherently improper about interactions between industry and individual physicians/institutions but these interactions must be more transparent.

The potential common ground: restoring trust through greater transparency

More transparent transactions and interactions will be necessary for individual physicians and institutions and industry to collaborate in a manner that yields the greatest results. As industry, private and public physicians, and the government continue to grapple with this issue, all must be willing to report and disclose material relationships. A national extramural database, a corollary to the clinical trial registry, may be a critical

starting point to centralize the activities of those who: (1) receive federal research funding or medical services reimbursement of any kind and (2) have financial relationships with industry above a certain threshold. Activity type, consulting compensation, primary funding organization, date, duration of activity, etc. would be reported. The AMA and PhRMA, organizations representing two major stakeholders, could collaborate to develop the reporting criteria and scheme while the PhRMA could take the lead in developing and managing the reporting system. Such a reporting system would be the beginning of a tangible and good faith effort to address the central issue. However, to enforce reporting compliance, transformational commitment or the renewal of the health care provider oath may be required. As the depth and breadth of these relationships is revealed, it may become apparent that prominent researchers, clinicians, and academicians, who consult with numerous parties, are not indebted to any one organization. Similarly, those who have periodic engagements with organizations in their therapeutic area of expertise are not likely to be perceived as agents of the companies with which they consult. On the other hand, those who have very narrow and deep financial relationships, who may in fact be acting as an agent or employee of the commercial interest, would need to significantly alter their relationships or have these relationships exposed.

Conclusion

Despite tremendous progress against disease and illness, a great deal of work remains in the years ahead. The incidence of infectious and cardiovascular disease, obesity, diabetes, kidney disease, and stroke, to name a few, are predicted to increase dramatically in the next decade. Neither industry nor organized medicine is capable of handling these daunting challenges alone. To take the fight against illness well into the 21st century, especially as the US population ages at an unprecedented rate, transparent teamwork and collaboration between the health professions and the health care industry will be required and policies or approaches that sever vital interaction with industry are neither strategically sound nor appropriate.

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