Review Article

RELATIONSHIPS BETWEEN HEALTH PROFESSIONALS AND THE PHARMACEUTICAL INDUSTRY: ACHIEVING A BALANCE

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ABSTRACT

Health professionals and the pharmaceutical and medical-device industry have had a long and often problematic relationship. The interaction between for-profit companies trying to promote and market their products and the prescribers of those products has come under increasing scrutiny. Most of the current regulation is from the industry's side; health professionals and professional medical associations are taking much longer to disentangle themselves from this often unethical relationship.

Keywords: health professionals, pharmaceutical industry, conflict of interest, professional medical associations

INTRODUCTION

> The integrity of the relationship between the providers of a service or a product on the one hand and their customers or consumers on the other, has always been an eclectic minefield of conflicting and provocative market and ethical forces. Moreover, when such a relationship is nurtured between the providers of health care services … and corresponding commercial concerns, the issues arising from the abuse and potentially manipulative deceits of such relationships necessarily stand out in sharp focus.[1]

Pharmaceutical companies play a vital role in the healthcare chain. Expensive medical therapies and devices would never reach patients without the research and development funded by the industry. The rapid development of effective vaccines against COVID-19 would not have been possible without multinational pharmaceutical companies. However, pharmaceutical companies are businesses and the large ones are owned by shareholders who expect financial returns on their investments. Historically, there have been numerous examples of corruption and antitrust involving some of these companies.[2] In addition, medical professionals and their professional societies have had a co-dependent and often unethical relationship with the industry.

In this article we raise some of the troublesome issues with a view to discussing ways of managing such relationships in a way that fulfils moral and ethical responsibilities and benefits the recipients of healthcare, namely, our patients.

DEFINITIONS APPLICABLE TO RELATIONSHIPS BETWEEN HEALTH PROFESSIONALS AND INDUSTRY[3,4,5]

Industry refers to the full range of institutions and enterprises with a bearing on healthcare, distinguished from the actual work carried out by health professionals in their clinical and research practice.

An *interest* is a commitment, goal, obligation or value associated with a social relationship or practice.

Where two or more distinct interests coexist in a particular decision-making setting, a *duality of interests* is said to exist.

When a relationship or practice gives rise to two conflicting interests, *a conflict of interest* exists. The precise condition that defines the presence of a conflict of interest is that in relation to a specific decision or action, two opposing and contradictory interests, as defined above, coexist.

A *pecuniary interest* refers to the possibility of financial or other material gain arising in connection with professional decision-making.

A *non-pecuniary interest* is a goal or benefit not linked directly to material gain.

A *conflict of interest* is a set of conditions in which professional judgement concerning a primary interest (such as patients' welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).[4]

It is a condition, not a behaviour.[5]

THE PHARMACEUTICAL INDUSTRY: FRAUD, SCANDALS AND DUBIOUS PRACTICES

The global pharmaceutical industry has been termed 'Big Pharma'. The top companies make billions of dollars every year, but they have also been involved in fraud, scandals and other dubious practices that have resulted in lawsuits, fines and the withdrawal of drugs post-marketing.[6]

The pharmaceutical industry would have us believe that the cost of drugs is fuelled by the research and development (R&D) of new drugs. In reality, for every US$1 spent on 'basic research', Big Pharma spends US$19 on promotions and advertising.[7] According to Drugwatch:[6]

> From 1998 to 2016, Big Pharma spent nearly $3.5 billion on lobbying expenses — more than any other industry.
>
> In 2016 alone, it spent about $246 million. That's more than the defense industries and corporate business lobbyists combined.

One of the biggest scandals in recent years was that of Vioxx® (rofecoxib), an anti-inflammatory manufactured by Merck, which was linked to an increased risk of cardiovascular events and deaths after it had been marketed. It took the company four years to withdraw the drug from the market, during which time its use is estimated to have resulted in between 30 000 and 55 000 deaths, according to a researcher with the US Food and Drug Administration (FDA), Dr David Graham.[8] Merck pleaded guilty to criminal charges related to the marketing and sales of Vioxx® in 2011 and paid billions of dollars in fines and compensation to patients and their families.[6]

GlaxoSmithKline paid US$3 billion in 2012 after pleading guilty to criminal and civil charges related to its popular antidepressant Paxil® (paroxetine), marketed off-label as a treatment for children younger than 18. Similarly, Johnson & Johnson (J&J) promoted its antipsychotic drug Risperdal® (risperidone) off-label for ADHD, anxiety, sleep difficulties, depression and behaviour disorders in children and the elderly. It resulted in increased deaths from heart disease and strokes in elderly patients, and gynaecomastia in adolescent males. In 2015, Austin Pledger was awarded US$2.5 million after the jury in the first Risperdal® trial determined that J&J had failed to warn about the risk of gynaecomastia.[6]

In her book, *The Truth About the Drug Companies*, Marcia Angell discusses the deceptions perpetrated by the pharmaceutical industry.[9] She points out that the drug companies produce very few innovative medicines and that this has led to a reduction in their profit margins. Previously they were at the top of the Fortune 500 list in the United States, but they have fallen behind oil and gas companies, and big banks. One of the ways in which they try to extend patents on drugs and ensure profits is by making 'me-too' medicines that are variations of innovative drugs marketed in the late 1900s.[9]

PEDDLING INFLUENCE – HEALTH PROFESSIONALS

In his book, *Hooked: Ethics, the Medical Profession, and the Pharmaceutical Industry*, Howard Brody wrote:

> Stemming from a culture of entitlement based on the medicine–industry relationship, physicians attending the professional societies' meetings come to expect low registration fees, luxurious accommodations, and free dinner and entertainment each night. If societies were to hold their meetings in less accommodating means, attendance by physicians would be expected to drop.[10]

South African health professionals, in particular doctors, have a long-standing culture of entitlement that begins during their medical school years. Over the years, the industry has sponsored numerous doctors to attend international congresses. Not only did they cover registration, travel and accommodation expenses, but their guests were also wined and dined every night. Academics were included as they were seen as 'key opinion leaders' (KOLs) and able to influence the prescribing habits of their colleagues. Private-practice specialists benefited as they were the prescribers. Over the years, with dwindling marketing budgets and strengthening internal regulation of industry activities, the focus has shifted to sponsoring the high prescribers in private practice to attend international meetings. Much more cost-effective for the industry is sponsoring local congresses, meetings and symposia, paying honoraria and getting KOLs to hard-sell new drugs or approaches to treatment.

Another way of peddling influence is by having industry representatives detail drugs to doctors. Agarwal and Kaur[11] express their concerns:

> One of the key concerns of any health care system is the maximization of the health and well-being of its people. … One of the ways in which health care systems ensure that patients receive drugs that are both safe and effective is by requiring that physicians act as gatekeepers to certain classes of drugs. … In order to be able to make the best prescription decisions, physicians must have sufficient information about available drugs.
>
> While there are many prescribing information resources available to physicians such as formularies, medical journals, pharmaceutical company representatives, promotional packages, and other physicians, evidence suggests that direct to physician promotion by pharmaceutical companies has a significant effect on the number of prescriptions written for a drug. Undoubtedly, many of the promotional activities undertaken by pharmaceutical companies are vital sources of information for physicians and have immense educational value, but at the same time, there is genuine concern that these interactions may unduly influence prescription behavior and compromise physicians' integrity.[11]

Studies done in high-income countries reporting interactions between doctors and pharmaceutical companies and the effect on their clinical practices were analysed in a systematic review and meta-analysis.[12] Fifteen out of 19 studies that met the inclusion criteria found an association between interactions that promoted a drug and inappropriately increased rates of prescription of that drug, poorer quality of prescribing and/or higher prescribing costs.[12] Another systematic review demonstrated that the behaviour and prescribing habits of doctors who interacted with

industry representatives and/or accepted gifts from the company were influenced by these interactions and this led to higher prescription rates and irrational prescribing of the company's drug.[13] A systematic review of studies in low- and middle-income countries found that doctors felt the interaction with industry had a minor impact on their own behaviour and prescriptions and felt that they derived benefit from it.[14] This illustrates that the medical profession is appallingly ignorant regarding how biased the information provided by pharmaceutical representatives is and the influence that this information has on their prescribing habits.

PEDDLING INFLUENCE – PROFESSIONAL MEDICAL ASSOCIATIONS (PMAs) AND ACADEMIA

Professional medical associations (PMAs) play an important role in medical care in their areas of expertise and specialisation. The roles are listed in Table I. Because of these important roles, PMAs should be above reproach and free of any undue influences.[15]

The interactions between PMAs and industry tend to create conflicts of interest. These may be both real and perceived.[15] The concern is that industry funding of PMAs is pervasive:

- funding of annual congresses;
- sponsorship of invited speakers;
- paid satellite symposia at congresses;
- honoraria for lectures; and
- sponsorship of health professionals to attend congresses.

The last of these includes travel, registration, dinners and sponsoring social activities. At congresses the companies have exhibition booths with information about their products. The company representatives interact with attendees, distributing information leaflets and branded gifts.

Other ways in which industry funds PMAs is by sponsoring accredited continuing medical education (CME) or continuing professional development (CPD) activities, advertising in medical journals, supporting the printing of guidelines and handbooks, sponsorship of research awards and training sponsorships such as fellowships in academic units.[15]

In addition, the leaders of professional societies and influential academics frequently have close ties to industry. As an example, most of the Board and Science Committee members of the Global Initiative for Asthma (GINA) have received industry-funded grants and lectureship fees and/or they are advisory board members of companies.[16] As mentioned above, this does not necessarily indicate undue influence by the industry but it may constitute a conflict of interest. A study investigating the nature and extent of financial relationships between leaders of influential professional medical associations and the industry in the United States found that 72% of 328 leaders had financial ties to industry. Total payments amounted to US$130 million, with a median amount for each leader of US$31805 (interquartile range US$1157 to US$254272). 'General' payments, including those for consultancy and hospitality, amounted to US$24.8 million; research payments, predominantly to academic institutions where association leaders were principal investigators, amounted to US$104.6 million. There was great variation among the associations, with the American Society of Clinical Oncology (ASCO) being by far the highest beneficiary.[17]

TABLE I: ROLES OF PROFESSIONAL MEDICAL ASSOCIATIONS[15]

1. Medical education
   - Congresses, meetings, publications, journals, CME
   - Promoting standards for a discipline or specialty through influencing curricula
2. Practice guidelines – evidence-based information and recommendations
3. Defining ethical norms for members
4. Public agenda: advocate on behalf of members, patients and best interests of society
5. Represent expertise and authority to those inside and outside medicine

Regarding research, most clinical trials receive funding from industry with a view to registering drugs and devices in the commercial environment. This could result in bias in the way in which the trials are planned, conducted and funded, and ultimately published and reported on. Many senior academic researchers have units that are funded wholly or partially by the industry.[18] Authorship of articles in top medical journals is earned according to the number of patients recruited for a clinical trial, and the articles are frequently written by ghostwriters.[18] A Cochrane review published in 2017 found that industry-sponsored drug and device studies tended to arrive at more favourable results and conclusions than studies with sponsorship from other sources.[19]

It is essential to maintain the relationship between academic opinion leaders and the pharmaceutical industry to ensure that both parties operate effectively and for patients ultimately to achieve the most benefit. Nevertheless, it is precisely within the culture of this co-dependent relationship that many opportunities for irregular enrichments have occurred. Some common dynamics and specific examples of these perverse opportunities are: KOLs being preferentially invited to participate in clinical trials in their institutions with a specific new chemical entity (NCE) and being paid hefty investigator fees; and after that serving as members of advisory boards and academic advocates at the subsequent drug launch.

PEDDLING INFLUENCE – PATIENT ADVOCACY GROUPS

Many patient advocacy groups receive funding from the industry. A survey conducted in the United States revealed that two-thirds of patient advocacy groups were partially funded by industry.[20] A United Kingdom study showed that 508 patient advocacy organisations received industry funding between 2012 and 2016. Most of the funding was for cancer organisations, with diabetes and other endocrine disorders among the second most funded.[21]

In 2007 Mylan hiked the price of the adrenaline auto-injector used to treat anaphylaxis (EpiPen®) from less than US$100 to more than US$650. Neither of the two prominent patient advocacy groups in the United States, Food Allergy Research & Education (FARE) and the Asthma and Allergy Foundation of America (AAFA) spoke out against the company, nor did they inform their members about cheaper alternatives.[22,23]

Many patient advocacy groups have limited or no information on

their websites regarding corporate funding. A study published in 2006 looked at ten health conditions represented by groups in five countries, including seven organisations in South Africa: cancer, heart disease, diabetes, asthma, cystic fibrosis, epilepsy, depression, Parkinson's disease, osteoporosis and rheumatoid arthritis. The authors found that the websites provided insufficient information for readers to be able to assess whether a conflict of interest with industry exists. While advertising products was uncommon, the websites clearly displayed company logos and corporate advertisements.[24]

'PHYSICIAN, HEAL THYSELF'

Most of what we have written so far suggests that the industry is wholly to blame for the entanglement with health professionals – but this is patently not true. Abbasi and Smith wrote in a *BMJ* editorial:

> Drug companies are commercial companies that must market their products. Sometimes they bend the rules, but it is doctors who are perhaps more to blame in coming to depend on drug company largesse. How did we reach the point where doctors expect their information, research, education, professional organisations, and attendance at conferences to be underwritten by drug companies?[25]

We know of colleagues who accepted sponsorships from more than one company to attend international congresses, using funding from one for travel expenses and pocketing the funds from the other. We are also aware of colleagues who threatened to stop prescribing certain drugs if the company did not sponsor them to attend a congress. Academic departments and professional societies' journal clubs regularly benefit from company-sponsored meals under the guise of learning about new products.

STRADDLING BOTH WORLDS

One of the present authors has been most fortunate to have straddled more than one professional activity, many of these functions being enjoyed simultaneously. Some of these activities related to his medical career in practice, clinical research and academic medicine, and some have related to other positions where he enjoyed senior and decision-making roles in business, corporate and institutional structures. In these roles, it has perhaps been easier to have been able to observe examples of perverse incentives, ethical misdemeanours and corruption from many different sides of the proverbial 'fence'.

Many have, of course, argued that it should have been impossible for anyone to act fairly and in an unbiased way if they were serving many 'masters' or had conflicting objectives at the same time. For example, how could anyone act from the perspective of medical academic KOLs while at the same time performing a decision-making role for a commercial and marketing company? More specifically, during many years as a Senior Regional Executive Vice-President of two of the largest global multinational pharmaceutical companies, working across four continents, the author was at the same time also an active academic with adjunct professorial roles at two medical schools. Simultaneously, he occupied a position as the non-executive chairman of a financial services and insurance company and was concurrently an active Senate member of the Colleges of Medicine of South Africa. At the same time, he also served as the chairperson of some special interest medical societies.

In all co-dependent relationships, by definition, an enhanced potential exists for the emergence of dishonest and usually surreptitious and covert behaviours designed to favour one or other party. This pattern is designed to maintain and nurture the propensity for these usually perverse relationships to survive, since the symbiotic nature of any such dynamic is based on strong interconnected benefits for both parties. These benefits are often not honourably obtained and range from moot ethical misdemeanours to gross corruption.

The hallmark of these behaviours is that one or the other of the parties is fully aware that their actions would not pass what is popularly called the 'CNN' ethical litmus test (ie to be comfortable that any of their actions would be broadcast to the world, transparent and beyond any negative judgment or reproach). These bad behaviours are consequently neither declared nor transparent.

To provide some context, in today's commercial and business world, the 'profit and shareholder enrichment model' describes how, on the one hand, one typically has a manufacturer, a producer of goods and services, who has a duty to its shareholders to sell their products using every conceivable tool in their toolbox to achieve the optimal sales and profit margins for their goods, using various and every eclectic sale and marketing technique. On the other hand, the potential buyer or customer is authentically approached by the seller in various ways to conclude a procurement transaction which would in the end benefit both parties. These modern-day sales and marketing techniques predicate the reality that the seller's job is licensed to go out of its way to please, cajole and even remunerate the potential customers in diverse ways such as pricing competition, offering bonuses or even 'in-your-face' accostments to conclude the sale or use of their product.

But in the medical world, where the safety and care of our trusting patients dominates the logic of our decisions, frank and comparative advertising and selling has thankfully recently (within the past three decades) been subject to increasingly stringent marketing regulations. In South Africa, those promotional guidelines are provided by the South African Health Products Regulatory Authority (SAHPRA). Certainly, in this country, product-scheduling clearly lays down what is acceptable regarding the extent and nature of the various medical sales and marketing practices available to pharmaceutical companies. For example, Schedule 0, 1 and 2 products and drugs allow permissible detailing direct to the public, such as that for 'over the counter' and 'consumer' branded advertising. But medicines from Schedule 3 and above are open only to specific detailing and advertisements aimed directly at the healthcare professional (HCP) under rigidly controlled circumstances. This regulatory framework sets the tone for a responsible and healthy relationship between pharmaceutical companies, the public and the HCP.

Regrettably, this regulatory clarity which defines the rules for the

responsible marketing of scheduled drugs seems to be far less clear when one digs a little deeper into the myriad other, more shadowy and less defined transactional partnerships between participants in the broader Health Care Delivery System (HCDS) and value chain. And this is where corrupt practices and ethical malfeasance have their roots.

There are many ways to 'skin a cat' and over many decades new and inventive ways in which to incentivise doctors to prescribe and use specific products have gradually been devised and practised, to the extent that many of these practices have over past decades become the new norm in the HCDS and among its various stakeholders. But this does not imply that these emerging norms are either ethical or acceptable. Nevertheless, these practices have continued and have even developed an aura of respectability in many cases. The mantra that 'everybody is doing these things so it must be OK for me' rings loudly and clearly when some dubious practices are suggested to vulnerable partners.

MANAGING RELATIONSHIPS

Regulation of the pharmaceutical and medical-device industry occurs through national legislation, self-regulation by organisations such as the Pharmaceutical Research and Manufacturers of America® (PhRMA)[26] and the Marketing Code Authority (MCA) of South Africa,[27] and individual companies' guidelines and codes of practice. Clinical trial registers have been established to promote transparency.

We wish to shift our focus to the way HCPs and professional medical associations should manage their relationships with industry. It is in the interests of patients and society for us to work together, but we need to disentangle. The time has come for us to review the way we fund our societies and congresses, and to recognise when a relationship is problematic.

The Royal Australasian College of Physicians (RACP) established guidelines to help manage health professional–industry relationships.[3] The document includes algorithms aimed at questions and settings in which conflicts of interest may arise. The authors suggest using four 'generic tools' to help HCPs to:

- recognise when there could be a real or perceived conflict involving interests of the profession and those of for-profit organisations;
- distinguish between a duality and a conflict of interest (as defined above);
- manage possible and established conflicts of interest; and
- confirm that they are comfortable with establishing, continuing or changing the terms of a relationship with a for-profit organisation.

The four tools are summarised in Table II. Each tool has a set of questions that deals with various role conflicts, financial relationships and personal relationships that may affect decision-making or discussion. If any of the questions return a 'yes' answer, the HCP is advised to consider discussing the issue with colleagues and/or professional societies or organisations.[3]

The medical profession must regulate the role of the pharmaceutical representative in detailing doctors in their consulting rooms and at congresses. This constitutes product promotion, not education, and gives the industry excellent access to medical professionals. The pharmaceutical representative's role should be to provide support and access to literature on request, and to provide pharmacotherapy education.

TABLE II: GENERIC TOOLS TO HELP HCPs ASSESS RELATIONSHIPS WITH INDUSTRY[3]

Tool 1: Identification of dualities
Tool 2: Identification of conflicts of interest
Tool 3: How should this conflict of interest be managed?
Tool 4: Additional questions to be considered before initiation, continuation or change of a personal or organisational relationship

The use of brand names in prescriptions must be discouraged because this reinforces the influence of companies on prescribing habits. Only international non-proprietary (INN) or generic names of medications must be legally permitted on prescriptions. This will serve to disentangle the relationship between medical professionals and Big Pharma.

Rothman et al published an article in 2009 in which they proposed ways in which PMAs may deal with conflicts of interest with industry.[15] They point out that avoiding all relationships with industry is neither feasible nor sensible. However, gifts, even those of limited value, create a sense of obligation and can bias HCPs' choices. PMAs should establish guidelines in which various types of conflict of interest are explained and dealt with. And educational activities must certainly be distinguished from marketing.

The authors make several recommendations aimed at controlling conflicts of interest in PMAs. They advise that associations should aim for total financial independence of industry, apart from pharma advertising in medical journals and sponsoring congress exhibition fees. Obviously, this cannot be implemented all at once but it should be introduced gradually. Industry must not be able to influence the choice of topics or speakers for congresses and meetings, and all committee members and speakers must disclose their financial ties to industry. This disclosure should not be treated as a joke, as has happened at some of our meetings where the speaker says, 'if your company's name is not on the slide, come and see me after the session!'

Promotional gifts should not be permitted; PMAs must not endorse companies' satellite symposia; industry sponsorship of research should be delinked, with funds going into a central repository; research applications should be peer reviewed without industry involvement; and industry funding for fellowships and training should also not be linked to an individual company. Regarding the formulation of practice guidelines, Rothman et al point out that disclosure of industry relationships by guideline authors is insufficient protection to ensure the independence of either actual or perceived industry influence. This is probably one of the most difficult issues to resolve, as most medical professionals serving on guideline committees have or have had some kind of relationship with industry.[15]

Journal advertising should be independent of the content of the journal and industry should not fund practice guidelines. PMAs must not endorse commercial products or services. To avoid any conflict of interest, office-bearers and board members of a PMA must not derive any personal income or research support from industry during their tenure. Regarding affiliated foundations, the authors state:

> Many PMAs have established affiliated research and education foundations that share their name and their mission. Although separate from a governance and taxation standpoint, these organizations are generally closely aligned with and indistinguishable from the parent PMA. Accordingly, the affiliated foundation must be held to the same standards on conflict of interest as the parent PMA. ... Moreover, in accepting funding directly from its affiliated foundation, the parent PMA is not absolved of the need to avoid or minimize conflict of interest.[15]

CONCLUSION

The pharmaceutical and medical-device industry is important in ensuring medical progress and the development of new drugs and devices. HCPs and industry are inextricably linked but must become disentangled. Co-dependent relationships will always provide situations which encourage dishonesty and perverse behaviours between some participants, who are tempted to extract personal benefit from various interactions and opportunities, even at times breaching ethical and moral standards. Fortunately, many effective checks and balances have been introduced by all those parties who are eager to regulate and audit the ethical behaviours of their own institutions and companies. Everybody recognises that maintaining these relationships is essential if the ongoing partnerships between all the stakeholders are to remain fruitful and effective in nurturing the growth of our scientific and service-oriented health culture and value proposition. Doing so is ultimately to the benefit of our patients, whom we all serve and care for. Much hope and comfort lie in that recognition.

We end this article with two quotes that illustrate the difficulties and potential pitfalls in health professional–industry relationships. The first is by Ian Roberts-Thomson from an editorial in *JGH Open*:

> Despite laws, industry codes, self-regulation by industry, and guidelines by medical organizations, gastroenterologists and hepatologists will continue to encounter circumstances that involve ethics and conflicts of interest. Important progress has been made, but we need to be vigilant in avoiding impropriety and the appearance of impropriety while, at the same time, interacting with industry in ways that are both respectful and professional.[28]

The second is from Santosh Soans, the national President of the Indian Academy of Pediatrics (IAP):

> Indeed we are living in a world of contradictions galore and it is agonizing to make sense of it all. In the final reckoning, one can only say that it is left to the individual to decide where to draw the line. The choice is between self-respect and greed, professional autonomy and obligation, patient well-being and self-gratification. Choosing the formers has the power to elevate you, falling prey to the latter ones can potentially destroy you. May wisdom prevail in every decision you make.[29]

May we have the wisdom in future to deal honestly with our conflicts of interest and to be open, respectful and honest in our dealings with industry, in the best interests of our patients.

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CONFLICT OF INTEREST

SK has received honoraria for talks from Sanofi and AstraZeneca, and is a member of the Executive Committee of ALLSA. MH is the Lead Independent Non-Executive Director of Adcock Ingram Holdings.

This article has been peer-reviewed.

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