

Undue influences on drugs and device industries distort healthcare research, and practice

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ABSTRACT: Background: Expenditure on industry products (mostly drugs and devices) has spiraled over the last 15 years and accounts for substantial part of healthcare expenditure. The enormous financial interests involved in the development and marketing of drugs and devices may have given excessive power to these industries to influence medical research, policy, and practice. **Material and methods:** Review of the literature and analysis of the multiple pathways through which the industry has directly or indirectly infiltrated the broader healthcare systems. We present the analysis of the industry influences at the following levels: (i) evidence base production, (ii) evidence synthesis, (iii) understanding of safety and harms issues, (iv) cost-effectiveness evaluation, (v) clinical practice guidelines formation, (vi) healthcare professional education, (vii) healthcare practice, (viii) healthcare consumer's decisions. **Results:** We located abundance of consistent evidence demonstrating that the industry has created means to intervene in all steps of the processes that determine healthcare research, strategy, expenditure, practice and education. As a result of these interferences, the benefits of drugs and other products are often exaggerated and their potential harms are downplayed, and clinical guidelines, medical practice, and healthcare expenditure decisions are biased. **Conclusion:** To serve its interests, the industry masterfully influences evidence base production, evidence synthesis, understanding of harms issues, cost-effectiveness evaluations, clinical practice guidelines and Healthcare professional education and also exerts direct influences on professional decisions and health consumers. There is an urgent need for regulation and other action towards redefining the mission of medicine towards a more objective and patient-, population- and society-benefit direction that is free from conflict of interests.

Keywords: undue influence, conflict of interests, evidence-based medicine, healthcare industry, medication, pharmaceutical industry.

INTRODUCTION: A universal characteristic of most healthcare systems in developed countries is the heavy focus on pharmacological approaches for treating and preventing chronic disease and the considerable expenditure on high-tech medical equipment, devices and technologies. This focus is often linked to astonishing financial interests, such as the \$130 billion a single drug (Lipitor) generated over 14 years¹ an amount that is higher than the 2010 gross domestic product of 129 of the 184 countries in the world². Besides traditional drugs, biologics and devices can also produce huge revenue. For example, the manufacturers of anti-TNF biological drugs and therapies have created a \$10 billion annual market^{3,4} even though these agents are used for indications with rather modest, incremental benefits. The market for drug-eluting stents for coronary artery disease is \$4.6 billion per year in the United States alone⁵, even though a large share of the indications for which these stents are used (e.g. stable coronary disease) has no supporting evidence⁶⁻⁹. This excessive financial capacity and the associated political and lobbying power allow the industry to dictate the rules of the healthcare game to serve its interests at several levels. The industry's interests are often at stark contrast to those of the patients and the society. In this article, we try to analyse the multiple complex pathways through which the industry has directly or indirectly infiltrated healthcare systems including strategic direction, expenditure, research, medical education and daily clinical practice.

HOW THE INDUSTRY INFLUENCES HEALTHCARE RESEARCH, STRATEGY, EXPENDITURE AND PRACTICE: The industry has created means to intervene in all steps of the processes that influence healthcare research, strategy, expenditure and practice. These include evidence base production, evidence synthesis, understanding of harms issues, cost-effectiveness evaluation, clinical guidelines formation, healthcare professional education and direct influences on healthcare professional decisions.

Evidence base production: Industry funds and often designs and controls a large portion of the most influential medical studies. Trials funded by for profit organizations are on average 4 times more likely than trials sponsored by non-for-profit organizations to favour the sponsored drug^{10,11}. Empirical evidence suggests that while methodological quality is the same in industry-sponsored and other trials¹⁰, industry-sponsored trials are more likely to compare the sponsored intervention against an inactive or straw man comparator^{3,10}. An evaluation of over 600 trials registered in clinicaltrials.gov shows that with few exceptions, single trials address only products of a single company¹². However, for most conditions, there exist many possible interventions, including lifestyle changes and products manufactured by diverse companies. Finally, for many years now, the public sector has largely abandoned the conduct of randomized trials to the industry and thus, not surprisingly, the most cited trials are almost always industry sponsored, often exclusively so¹². These trials then also guide the conduct of other clinical research. Medical research is doomed to navigate only questions posed by the industry and their extensions. There is increasing direct evidence about the manipulation of reported results in industry-sponsored trials, which demonstrate favourable results and the avoidance of inconvenient findings, as in the case of gabapentin for off-label use¹³. In addition to these direct biases, the industry has a major impact on which research is published in the most influential medical journals through ghost authorship^{14,15}, (i.e. raising the status of trial results by listing academically affiliated investigators as first or second authors in manuscripts) written by company staff or professional medical writers paid by the companies. It is possible that major journals have often undisclosed conflict of interests from publishing industry trials. Journals also have conflicts themselves, because such industry trials generate considerable revenue from offprints and can boost the journal's impact factor by as much as 15%⁶.

Evidence synthesis: Systematic reviews that summarize trials addressing the wrong questions (as above) will simply reinforce the wrong messages¹⁷, unless meta-analysts are astute to diagnose the problems in the generation of the evidence, let alone publication and other selection biases. Access to raw data of clinical trials to date has been limited, and integration in systematic reviews of the data that are readily available may perpetuate and solidify the biases of the primary literature¹⁸. Moreover, as systematic reviews and meta-analyses have grown in prestige and influence, the industry has also infiltrated this type of research. A systematic review comparing the methodological quality of meta-analyses of the same drugs by source of funding (industry-funded verses nonindustry funded)¹⁹ concluded that the former type of study is of lower methodological quality and considerably more likely to omit reporting bias-relevant details (e.g. descriptions of the excluded patients/studies). Although the estimated treatment effects were similar on average, 100% of industry-funded meta-analyses had conclusions recommending the experimental drug without reservations compared with 0% of the (independent) Cochrane reviews¹⁹. In meta-analyses of antihypertensive drugs, financial ties to a pharmaceutical company were not associated with favourable results, but were linked to four times higher odds to report favourable conclusions²⁰. Furthermore, conflict of interests in the original studies included in meta-analyses are usually silenced and unreported²¹. For example, a recent study revealed that only 2 of 29 pharmacological metaanalyses reported the funding sources of the trials and none of them reported author–industry ties in the primary trials²¹. Finally, content experts who co-author systematic reviews and meta-analyses may often distort the phrasing of the research questions, the results and the interpretation of these reviews in favour of industry products²².

Understanding of harms issues: Licensing for new products or indications requires demonstration of effectiveness and absence of major harms. However, the whole process allows plenty of room for serious harms to be unrecognized by the time licensing is granted. Many interventions are withdrawn or acquire black boxes years after they are licensed and after they have already cost a fortune to the healthcare system²³. Recent drug withdrawals suggest that financial ties with the pharmaceutical industry can determine the orientation of the authors of trials and meta-analyses in drug safety issues. Rosiglitazone, a multibillion selling drug for type 2 diabetes, was approved and prescribed to millions of patients worldwide for 10 years despite limited evidence on its benefits and, especially, safety²⁴. Rosiglitazone potentially increases the risk of cardiovascular disease and comorbidities such as weight gain and increases blood lipids. It has recently been withdrawn from both the EU and New Zealand markets, and its indications have been severely restricted in the United States²⁵. Among the many similar revelations, perhaps the best known case is rofecoxib (Vioxx), a blockbuster non steroidal anti-inflammatory drug that nearly doubled the chances of both myocardial infarction and stroke²⁶. Data revealed during a litigation case suggested the manufacturer intentionally distorted the presentation of trial safety data²⁷ and trained its sale representatives to tactfully avoid physician questions on safety²⁸.

Cost-effectiveness evaluation: Cost-effectiveness of therapies is a major criterion when allocating scarce public resources and is directly influenced by commercial pricing strategies. Most published analyses report favourable incremental cost-effectiveness ratios, and studies funded by industry are more likely to report ratios below required thresholds on cost-effectiveness²⁹. Studies funded by industry are more than twice as likely to report cost-effectiveness ratios below \$20 000 per quality-adjusted life year compared with studies funded by other sources [30]. There are many different methods by which industry-sponsored cost effectiveness analyses can achieve more favorable results, including but not limited to biased assumptions about the intervention, its comparators (e.g. underestimating the sensitivity/ specificity of the standard Pap test for analyses of HPV vaccines or HPV DNA tests for cervical cancer prevention)³¹ or other parameters that need to be modeled (e.g. extent of indirect effects for vaccines)³².

Clinical practice guidelines: Clinical practice guidelines are supposed to be based on best evidence. They are endorsed by recognized authorities, and to a large extent, they define daily medical practice. Integrity, objectivity and independence are of paramount importance for a correct translation of the evidence into clinical guidelines. These three crucial attributes are difficult to safeguard. Most (56%) scientists involved in the 17 most authoritative US cardiovascular clinical practice guidelines released between 2004 and 2008 received research grants, honoraria for speeches in drug-promoting events, stocks (shares) or consultancy fees by pharmaceutical and related industries³³. Over 80% of the committee chairs had such conflict of interests. Over 50% of guideline panel members in the United States and Canada have conflict of interests while the respective figure for guidelines sponsored by nongovernment sources approaches 70%³⁴. Overall, between 56 and 87% of clinical practice guidelines, authors have been found to have at least a conflict of interest (consultancies, research support, equity/stock ownership)³⁵. There is substantial margin for the members of these committees to input their subjective views through 'expert opinion' (evidence level C), which represented nearly half of all major US cardiovascular clinical care guidelines published between 1984 and 2008³⁶. Even higher levels of interaction were noted between the authors of 44 clinical guidelines and the pharmaceutical industry in a previous publication³⁷. Given that the boundary between industry and academia has become so vague, it is hardly surprising that clinical practice guidelines often are heavily focused on new costly interventions and only loosely follow the available evidence. For example, current guidelines still advocate tight pharmacological glycaemic control for patients with type 2 diabetes, despite the best available evidence suggesting that there is no major benefit for patients³⁸ and possibly even deterioration of quality of life³⁹. Declarations of the conflict of interests of expert panels and researchers are thought to guarantee transparency and integrity in the evidence base and clinical recommendation generation process. Nevertheless, there appears to be a gap between the intended purpose and practice as financial conflict of interests are severely under-reported in drug trial meta-analyses and panel guidelines³⁴ and practitioners very rarely discount for such conflicts when evaluating the evidence base⁴⁰. Besides clinical guidelines formation, narrative review and editorials by key opinion leaders also have a major impact on clinical practice decisions and the medical community in general^{41,42}. An example of the influence of the conflict of interests of key opinion leaders is that although evidence does not support that brand-name drugs are superior to generic drugs⁴³, editorials often counsel against the interchangeability of generic drugs⁴³.

Healthcare professional education: Intense exposure to pharmaceutical marketing commences during undergraduate medical education for future prescribers. A study showed that third-year medical students are exposed to one industry-sponsored gift or activity per week and almost (93%) all have been asked or required to attend at least one industry-sponsored lunch⁴⁴. The large majority (67–92%) of medical students acknowledge that education from industry sources is biased and that pharmaceutical industry pressures increase over the course of medical school⁴⁵. This exposure brainwashes medical students' attitudes towards the marketed products⁴⁶. In the USA, 60% of medical school chairs have some form of personal relationship with industry (e.g. consultant, a member of a scientific advisory board, a paid speaker, an officer, founder or member of the board of directors)⁴⁷. Continuing medical education (CME) is an essential part of the development for practicing health professionals. In the United States, industry support for CME increased from \$301 million per year in 1998 to \$1.2 billion per year in 2007 accounting for approximately 60% of the total accredited CME costs (including advertising/exhibit payments)⁴⁸. Although there are signs of a reversing trend (due to regulatory restrictions and the economic trends), industry funded CME still accounted for approximately half of all CME by 2010⁴⁸. Industry sponsors have substantial influence over

the content of education programmes, which often involve hefty paid prominent medical figures presenting information about the company's latest products, often using slides provided by the company⁴⁹. Sponsored CME leads to increases in prescription rates by the attendant physicians of the promoted medication⁵⁰. In the UK, most hospital educational 'grand rounds' and many other medical education meetings are sponsored by the industry, with lunches provided in return for sales and marketing opportunities. In primary care, many staff events are sponsored by the pharmaceutical industry in return for a lunch and 'educational' opportunities on pharmaceutical products. Postgraduate education departments foster strong relationships with sales representatives, and educational meetings and conferences are nearly always industry financed⁵¹.

Direct influences on healthcare professional decisions: Direct marketing pressures by sales representatives are substantial, for example, a US cardiologist meets with sales representatives nine times a month on average⁵². In 2004, over a third of the \$57 billion that pharmaceutical companies spent on promotional activities went on visiting doctors to promote new drugs and establish relationships with health professionals in community or academic settings⁵³. Regular interactions with sales representatives increases the chances to add the drug company to a hospital's formulary by over 300%, and the combination of the physician receiving honoraria leads to even greater increases⁵⁴. The culture of industry-offered 'gifts' or equipment, educational textbooks, sponsorship or luxury travel⁵⁵ and free meals has been common across the entire spectrum of health practitioners. In many countries, most industries have a trade association representing their profit-orientated members, for example, the UK Association of the British Pharmaceutical Industry (ABPI) with 150 members, which has set up the Prescription Medicines Code of Practice authority to administer the pharmaceutical industries' own code of practice. However, there has been a recent exodus of ABPI members, with even fewer companies choosing to follow even this largely voluntary code [56]. Surveyed patients consider the financial ties between practitioners and drug companies unacceptable and a compromise to their quality of care⁵⁷; however, patients are rarely aware of their doctor's ties with the industry, which may have biased their care plan.

Direct-to-consumer advertising: In the United States, where such marketing practices are permitted by law, direct-to-consumer advertising (DTCA) is a major force of rising pharmaceutical costs⁵⁸. Industry spending on DTCA for pharmaceuticals alone increased from \$11 billion to \$30 billion within the 1996–2005 decade⁵⁹, about the same period of time when the total costs of prescription drugs were rising at a rate higher than 30% a year⁶⁰. Besides inflated costs for patients and healthcare providers [58], DTCA is linked to concerns over the aptitude of the lay public to understand risks and benefits through a 30-s TV or a one page magazine advertisement. DTCA typically commences one year after release of a new drug⁵⁹, which is a very short time frame for many unwanted side effects to become apparent. The US Senate has previously considered legislation prohibiting such advertising for at least two years⁶¹.

CONCLUSIONS: Given that many of the problems discussed above are closely linked to financial interests, we would argue that there is an urgent need to better deal with conflict of interests in medicine and healthcare. The Institute of Medicine has published a comprehensive set of recommendations on how to deal with conflict of interests in medicine so that the undue industry influences we describe above are eliminated⁶². These recommendations cover general policy measures, medical research, undergraduate and continuous medical education, medical practice, as well as clinical guideline formation. The evidence we presented highlights the case for tighter regulation on how the healthcare industry designs, conducts, disseminates and publicizes their research, markets their products and interacts with medical students, health professionals and researchers. Currently, industry expenditure influences and determines medical practice and attitudes at various levels at the expense of patients' health, healthcare budgets and medicine's integrity. There are positive signs of action taken in both United States and Europe, for example, the Sunshine Act in the United States that requires drug companies to declare all payments and hospitality or gifts they give to doctors. In Denmark, companies have been required to declare their payments to doctors since 2008, in Scotland, doctors have to declare such transactions themselves, and France is currently preparing such legislation. The New England Journal of Medicine banned cost-effectiveness evaluations sponsored by product manufacturers almost two decades ago. These are some indicative steps towards redefining the mission of medicine towards a more objective and patient-, population- and society-benefit direction that is free from conflict of interests.

CONFLICT OF INTERESTS: None of the authors have any conflict of interest to declare.

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