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Corporate influence over clinical research: considering the alternatives

This text is based on a presentation delivered during the annual Prescrire Awards ceremony in January 2012 by Marc-André Gagnon, PhD, Assistant Professor in Public Policy at Carleton University (Canada) and Research Fellow in Ethics at Harvard University (USA). Videos of the presentation (in French) are available online at english.prescrire.org, search with the terms "video" and "gagnon".

Abstract

● **The dominant business model of the pharmaceutical sector is based on the massive promotion of drugs that often do not represent any significant therapeutic advance.**

● **Clinical research is therefore run like a promotional campaign. The data obtained from clinical research are primarily used to boost and support sales rather than to improve prescribing behaviour.**

● **Three common and widely used corporate strategies are used to this end: ghostwriters are employed to inflate the number of publications showing the drug in a positive light; results that would harm sales are not published (publication bias); and negative data are suppressed, sometimes going as far as to intimidate troublesome independent academics and whistle-blowers. The objective of these strategies is to enable the new drug to gain market share from its competitors.**

● **If medicine is to progress, research must be more independent and freed from the commercial imperatives of the pharmaceutical industry.**

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Can we trust the results of clinical research as it is currently conducted? Since clinical research is mainly run by pharmaceutical companies, we cannot answer this question unless we understand the business model and the financial incentives behind the clinical research these companies conduct. We will therefore briefly analyse the predominant business model, which is based on massive promotion of drugs that too rarely represent any significant therapeutic advance, then we will analyse the nature of private-sector clinical research and explore the opportunity to develop a more independent approach to clinical research.

Profits without innovation

Between them, the 15 biggest drug companies share two-thirds of the global pharmaceutical market, worth 900 billion dollars. These companies spend about twice as much on promotion as on research (1). Their business model is based on the massive promotion of new drugs that often only extend an existing product line and offer no advantage over existing treatments.

A longstanding crisis in innovation. The vast majority of the new drugs introduced onto the market since 2010 provide no significant advantage over existing treatments. For over 30 years, *Prescrire* has been systematically analysing whether or not each new drug introduced onto the French market represents a therapeutic advance. By pooling all of the data collected since 1981, we can see that the proportion of drugs that represent no significant advance has been increasing, particularly in the last 10 years, as has the proportion of drugs with a negative harm-benefit balance (see figure 1) (**a**)(2).

For example, in 2009, *Prescrire* analysed 109 new drugs or indications (excluding generics): 3 were considered a minor therapeutic breakthrough, 76 added nothing new to the existing pharmacopoeia, while 19 were deemed to represent a possible public health risk (2). In Canada, the Patented Medicine Prices Review Board has been classifying newly patented drugs in a similar way since 2010. The results are comparable: nearly four-fifths of new patented drugs provide no therapeutic advantage over existing drugs on the Canadian market (3).

With innovation at a virtual standstill for decades, the pharmaceutical industry became conscious that it needed to change its model. However, the business model based on the massive promotion of drugs that are not truly innovative continues to thrive. It is quite simply the most profitable financial model. For example, the chairman of Sanofi-Aventis, Jean-François Dehecq, may well maintain that the "Pfizer model", in which twice as much is spent on promotion than on research, is now dead (4), but Sanofi-Aventis's financial reports show that in 2011 it still employed twice as many sales personnel as research staff. ▶▶

► **Profits continue to grow.** While standard economics might dictate that the market would penalise the lack of innovation in the pharmaceutical sector, drug company profits are actually soaring. It is difficult to conduct a historical analysis of the profitability of the global pharmaceutical industry because aggregated data are not available. However, 8 of the 15 major drug companies are American. Focusing on the dominant US pharmaceutical companies (from *Fortune* magazine's ranking of the 500 largest companies in the US) and comparing them with the other Fortune 500 companies, their rising average returns show that the sector is highly profitable (see figure 2) (**b**)(5).

The massive promotion of new drugs has a decisive role in ensuring that they are widely prescribed, even if they are no more effective than older drugs (5). Antipsychotics are a prime example of this. A "new generation" of antipsychotics was systematically prescribed by doctors, yet these drugs proved to be no more effective than the prior generation and were 10 times more expensive (6).

The current business model, based on aggressive promotion and meagre innovation, remains a huge financial success. Why would drug companies abandon it?

Institutional corruption of clinical research

In the current business model, pharmaceutical companies devote most of their resources to influencing medical practices rather than to developing and producing drugs. This involves generating medical knowledge tailored to support sales growth (5). Clinical research is therefore run like a promotional campaign, aimed at generating selling points to help market the product, rather than at putting out reliable scientific data (5,7).

To ensure that the scientific knowledge generated is profitable for the company, three corporate strategies are used to "ghost manage" research: the number of publications of studies that show the drug in a positive light is inflated; information that could harm sales is suppressed; independent academics are intimidated (or even "neutralised").

Inflating the number of favourable publications. Studies written for drug companies by ghostwriters do not come about as exceptions: they form part of carefully thought out publication plans that are essential to the success of promotional campaigns and the market launch of a new drug (8).

Here are some examples. Internal documents from Pfizer revealed that, between 1998 and 2000, the company directly initiated the writing of no fewer than 85 scientific articles on the antidepressant *sertraline* (Zoloft°). During this period, the entire scientific literature on this active substance consisted of only 211 articles (9). In this way, Pfizer produced a raft of articles showing the drug in a positive light, lessening the impact of the critical studies. Wyeth generated about 50 articles in favour of hormone replacement therapy (10). Merck mounted a ghostwriting campaign to promote its now-infamous drug *rofecoxib* (Vioxx°): 96 articles were published, some of which omitted to mention the deaths of patients who participated in clinical trials of the drug (11). GlaxoSmithKline ran a secret campaign to skew the literature in favour of its antidepressant drug *paroxetine* (Deroxat°, Seroxat°, Paxil°). They called it "Case Study Publication for Peer-Review", or CASPPER for short, in reference to the well-known "friendly ghost"... (12).

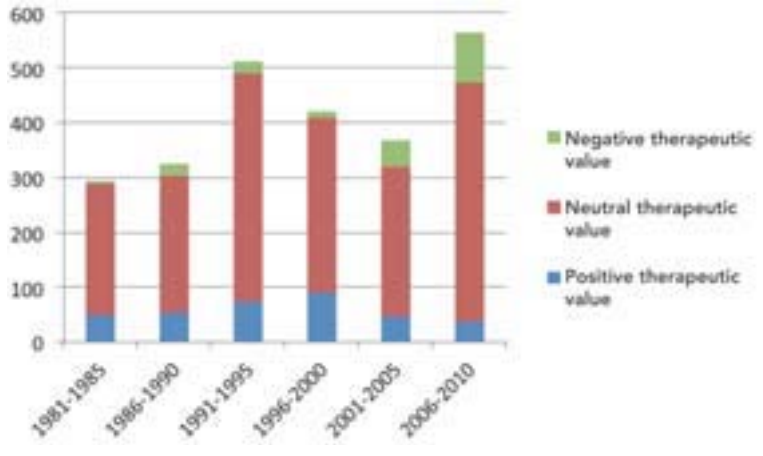
Suppressing the publication of results that could harm sales. Pharmaceutical companies consider that private-sector clinical research produces private, confidential results that are their own intellectual property. They assume the right not to publish certain results, in the name of trade secrecy. And they are not compelled by political and health authorities to make public the data obtained in clinical trials. Drug companies can therefore select which data they want to see published.

For example, major pharmaceutical companies have systematically failed to publish unfavourable studies on a "new generation" of antidepressants, the so-called selective serotonin reuptake inhibitors (SSRIs). Of the 74 clinical trials that were conducted on these antidepressants, 38 produced positive results, while the other 36 showed the drugs to have questionable or no efficacy. However, while 94% of the positive studies were published, only 8% of the unfavourable studies were published as negative results, and 15% of the negative studies were published in terms that suggested that the results were positive! (13). Doctors reading the scientific literature got a biased view of the "benefits" of SSRIs, which explains why they so readily systematically prescribed these antidepressants to their patients. The scientific data show that for 70% of the patients taking SSRI antidepressants, the drugs are no more effective than a placebo (14), but unlike a placebo SSRIs are associated with serious adverse effects (e.g. an increased risk of suicide).

Intimidating and even neutralising troublesome independent academics and whistle-blowers. A third strategy, which is more widespread that one might think, is to intimidate and neutralise independent researchers who produce studies that show the product in an unfavourable light. The case of Irène Frachon and *benfluorex* (Mediator°) is well known in France (15). But it is not exceptional. Merck's internal e-mails, which came out during lawsuits over the harm caused by its drug *rofecoxib*

Figure 1

***Prescrire's* ratings of new drugs and new indications since 1981**



Source : *Prescrire* (**a**)

a- *The categories used here are a simplified version of those used by Prescrire. "Positive therapeutic value" corresponds to a Prescrire rating of "Bravo", "A real advance" or "Offers an advantage". "Neutral therapeutic value" includes Prescrire ratings of "Possibly helpful" and "Nothing new". "Negative therapeutic value" equates to the Prescrire rating "Not acceptable".*

(Vioxx°), revealed that the company had drawn up a hit list of "rogue" researchers who had criticised Vioxx°. One e-mail recommended that the researchers on the hit list had to be "*discredited*" and "*neutralized*". "*We may need to seek them out and destroy them where they live*" read one of the e-mails. This intimidation was the result of the work of an entire team that systematically monitored everything that was said about the product (16). Similarly, in the case of the antidiabetic drug *rosiglitazone* (Avandia°), which was withdrawn from the market in 2010 for safety reasons, a report by the US Senate explained that the main strategy of GlaxoSmithKline executives when confronted with the publication of negative clinical results was to downplay the importance of these results and to intimidate independent researchers (17).

Figure 2

Average net profit margin of the dominant US pharmaceutical companies and other dominant US companies 1970–2010 (average over 3 years)

Source : Fortune magazine

In short. These three corporate strategies are ubiquitous. They corrupt medical research. It is an institutional, indirect form of corruption, acting through an economy of influence that pervades the whole of research and ultimately skews the scientific knowledge on which medical practice is based.

The vast majority of researchers are honest people who seek only to make a positive contribution to medicine, but because of the economic structures and the web of influence within which they operate, they often become unwitting pawns in a system in which shareholder profits are maximised at the expense of patient safety.

It would be inappropriate to blame drug companies for this state of affairs, because they have no choice. A company that refused to play the game for ethical reasons would rapidly lose its market share. In the current business model, pharmaceutical profits depend on the company's capacity to shape medical knowledge and create market niches, rather than to develop innovative treatments that improve patient health.

How can truly independent research be achieved?

Several fundamental reforms are needed in order to improve research practices. Transparency in clinical research is crucial; all of the results of clinical trials, whether financed by public or private funds, should be made publicly accessible. The regulation and elimination of conflicts of interest in medical research is also a main concern. Improvements could also be achieved by conducting a more rigorous clinical and pharmacoeconomic assessment of new drugs and linking profit margins to therapeutic value. However, the most urgent reform is to re-establish a high opinion for independent research.

The case for freeing research from drug company control. In the current situation, where short-term financial incentives shape research, a reliable way of ensuring profitability is to simply re-patent an existing drug. One need only alter the structure of the active substance slightly and mobilise an army of sales reps when the drug is launched to influence doctors' prescribing behaviour in favour of the "me-too" drug (**c**).

The pharmaceutical industry currently occupies a central role in all medical research, and public-sector research has merely a supporting role. There are some who feel that public-sector research is inferior, as if it were worthless without the involvement of the pharmaceutical industry.

Yet, clinical trials can only be free from any commercial considerations when conducted in an independent, not-for-profit research setting. And in fact, public-sector research already makes a huge contribution to drug discovery (18). A study published in 2011 revealed that, between 1998 and 2005, public-sector research contributed to the discovery of nearly two-thirds of the drugs that represented a genuine therapeutic advance, but contributed very little to the development of the products that provided no significant benefit relative to existing drugs (19).

Can we afford more funding for public-sector research? The question needs to be reframed, because contrary to popular belief, research is already largely funded from public sources. For example, once tax credits for research and development expenditure are taken into account, public funds pay for about 84% of basic health research, while the pharmaceutical industry contributes only 12% (20).

Governments also commonly offer a range of incentives to support their own pharmaceutical industry: direct subsidies, lax pharmacoeconomic assessments, extended exclusive rights, or generous pricing and reimbursement policies. For example, France offers the most generous system of tax credits for research and development (21), while Canada chooses to artificially inflate the price of patented drugs, where they cost about 10% more than in France. This policy adds about 1.5 billion Canadian dollars to the country's medicines bill, yet after tax credits have been taken into account, the pharmaceutical companies in Canada spend a net total of only 610 million Canadian dollars on research and development (22). In the US, public authorities do not intervene to reduce the costs of patented drugs. The prices are therefore double those in France. If the government allowed only one of the public health insurance schemes, *Medicare*, to negotiate minimal discounts on patented drugs, American taxpayers could save around 12 billion US dollars a year (23). ▶▶

b- For a detailed presentation of the methodology used and a more thorough analysis of the sector's profits, see reference 5.

c- A "me-too" drug, sometimes called a line extension, is a drug derived from an existing drug that is already marketed and often widely used, by slightly modifying the chemical structure of the active substance.

▶ Funding public-sector research should not be viewed as an additional cost, but as the means of reforming the expensive and ineffective current industrial policy.

In summary. As long as pharmaceutical companies hold the purse strings of biomedical research, medical knowledge will be selectively constructed for the purpose of marketing drugs rather than improving public health.

So long as public institutions continue to court partnerships with subsidised pharmaceutical companies, the way will remain wide open for the continued institutional corruption of scientific research.

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