Evolution of physician-industry relationships in producing knowledge of drug therapy - comparison of the United States and Finland

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Abstract

This paper presents a historical perspective on the evolution of relationships between the pharmaceutical industry and physicians in two countries, the United States and Finland. Despite divergence early the twentieth century, and the absence of any large pharmaceutical firms based in Finland, by the 1950s a similar partnership between medical experts and drug companies had developed. In the US, commercial influence in medical research can be divided into five periods: pre-reform (late 19th century – 1905), first reform wave (1905 - 1930), growing collaboration (1930 - 1945), merger of interests (1945 – 1950s, and second reform wave (1960s and 1970s). The history in Finland until the War was different: a preindustrial pattern persisted into the 'teens, followed by an interwar period in which the fostering of a domestic pharmaceutical industry was a national project and collaboration officially encouraged. After the Second World War the drug industry was no longer local, but the close physician-drug industry relationship largely continued as before. There are indications today that both countries have entered another reform period, this time international in origin. It is hoped that understanding of the origins and nature of relationships between biomedical experts and drug industry will help physicians offer better patient care.

Key words: drug industry, bias, research, history, sponsorship, United States, Finland

Running head/ short title: physician industry relationships

Introduction

Today most knowledge about the clinical effects of medicines is based on research funded or produced by drug companies. The aim of the companies is to sell their products, which at times conflicts with producing good science when that science can lead to a decrease in revenue. If the science is compromised the result is that confidence in medical knowledge is undermine (Bero and Rennie 1996; Kassirer 2006; Stamatakis, Weiler, and Ioannidis 2013). Evidence from the western countries shows that this conflict produces bias in research in various stages from design to publication (Lexchin 2012). Bias occurs in setting the research question/topic, choice of doses and comparator agents, control over trial design and changes in protocols, early termination of clinical trials, reporting to regulatory authorities, reinterpretation of data, restrictions on publication rights, use of fake journals, journal supplements and symposia, ghostwriting, publication and reporting of results and outcomes. These biases favor the studied drugs and thus the firms that produce them and often the sponsored clinical researcher as well.

Drug firms need biomedical scientists and academic physicians to produce the basic knowledge behind new drugs, and practicing physicians to enroll patients in clinical trials. Physicians are also an important target of drug marketing and research can be an effective marketing tool in itself. Thus, the relations between the drug industry and physicians, both as individuals and in the form of medical associations, are crucial for medical knowledge about treatment and therefore for the care patients receive.

The history of drug industry-physician relationship in medical research has received comparatively little attention because, as with current industry-physician relations, detailed information about the past

situation is hard to obtain. What little document-based history has been published largely concerns the United States (US). There is also a smaller body of literature concerning Germany, France, and the United Kingdom, all countries which are homes to large multinational drug firms. But has this type of relationship existed elsewhere in similar ways?

The purpose of this paper is, on the basis of selected historical literature, to summarize the development of the industry-physician relationship in the US from the late 19th century to the 1970s; and then to compare the development in the US to that of Finland, a country with a much different history of medical research. The information from Finland comes from earlier Nordic research on drug control (Bruun 1983; Bruun 1982; Hemminki and Falkum 1980) and individual case studies. In this way we illustrate common features in the two countries and the dependence of the development of the doctor-industry relationship on the context in which it occurs. Finally, by examining these experiences we offer suggestions for resolving the problems created by the current relationship between the industry and physicians.

Finland was chosen for comparison with the US because of existing research on the research culture in that country and because one of the authors (EH) is as active researcher in the field in Finland, and her experience and observations allow an interpretation of the Finnish experience. Finland is different from the US in many respects, including its relatively small geographical size and population, remote geography, low level of industrialization in the early 1900s, and not having had domestically based major drug firms. Also the Finnish position in the Cold War was much more neutral than other Western nations. Traditionally, publishing in international journals has been the norm for Finnish researchers. Initially, international connections and publishing were mainly with Germany, but after the Second World War these activities migrated to the English speaking countries, particularly the US. The rules of

international medical journals such as reporting potential conflict of interest and the ideology of US ethics committees have influenced national Finnish practices.

Summary of developments in the US

In the US, commercial bias in clinical research can be divided into five periods (approximate times) preceding the present era: rampant period from the late 19th century to 1905, the first reform wave from 1905 to the early 1930s, the midcentury courtship of academic medicine and the drug industry between 1930 and the Second World War, their marriage from the Second World War through the 1950s; and the second reform wave of the 1960s and 1970s, Table 1.

In the first period, a widely recognized problem in the US was a lack of standards in medical education and a large number of poorly trained physicians. The US was not the key country for medical research and the industry had little role in genuine drug research and development. Germany and France were considered the leading sites of scientific medicine. American drug firms were mainly selling old fashioned botanicals and so-called "patent" medicines (Liebenau 1987; Ludmerer 1985; Young 1989). But they were influential in producing and testing new drugs in clinical practice. Typical marketing methods to physicians were seeding or sampling trials, i.e., clinical "studies" that were mainly designed to introduce new medications to physicians. Testimonials were often collected by drug detail men (sales representatives) as favors against the provision of free samples or other benefits. Medical journals were financially weak and they allowed major advertisers to supply marketing content that posed as independent research reports (Marks 1997; Rasmussen 2004; Rasmussen 2005).

In the second period (1905-1930), various changes occurred both in medicine and the drug industry. The net effect was to create a subset of "ethical" pharmaceutical manufacturers interested in sourcing new drugs from scientific research, and willing to meet the new testing standards. Driving this was a strong reform movement within the medical profession that sought to raise the profession's standards and status under the banner of "scientific medicine" as practiced in Continental Europe (Ludmerer 1985; Starr 1982). In preclinical research, new scientific methods, developed mainly in non-commercial German laboratories, influenced US medical research, particularly after the First World War. In clinical drug testing, influential academic medical reformers imposed more rigorous scientific standards than previously. Systematic comparisons of drugs and publication of their results in journals became common by the 1920s. Placebo controls and double blinding were introduced (Lilienfeld 1982; Marks 1997; Parascandola 1992).

The American Medical Association (AMA) appointed elite committees to purge the profession of unscientific profit-driven "quacks" and to police the drug industry. The AMA Council on Drugs (originally Council on Pharmacy and Chemistry), consisting mainly of academic medical researchers, was founded in 1905. It collaborated with the editors of major journals to regulate journal drug advertising, in particular by requiring systematic safety testing and clinical trials for efficacy claims. Drug firms submitted preclinical and clinical evidence to the Council based on these trials and without its approval drugs could not be advertised in the cooperating journals. Along with this new scientific approach, the old testimonial tradition continued to exist and having friendly relations with these influential physicians was important to the drug industry in order to stimulate sales (Marks 1995).

The Council's approval system can be regarded as the predecessor and a model for the later Food and Drug Administration (FDA) premarketing drug approval system. Also, unless the Council specifically

allowed a drug to be advertised directly to consumers, it could be advertised only to physicians. In practice, this established a division between prescription and non-prescription drugs, which became federally regulated only in 1938. The FDA was created in 1906 with the authority to require purity and truthful labeling of drug products (Young 1989). There was also an attempt to establish an independent national institute to study drugs but it did not succeed (Parascandola 1992).

In the third period between 1930 and the Second World War, the role of the drug companies increased in drug research. Pre-clinical research collaboration between academic researchers and drug firms lost much of its disrepute and became normalized. Academic researchers initially did not consider patenting of medicines to be ethical, but now agreed to it and assigned intellectual property rights to firms (Rasmussen 2004; Swann 1988). In clinical research it became typical for drug firms to commission and even design clinical trials. Even eminent academic physicians conducted commissioned trials. In such trials, the firm also exercised significant control over publication, and studies often went unpublished if unfavorable to the product. When favorable studies were published, drug firms might purchase tens of thousands of journal article off-prints for distribution as marketing material (Rasmussen 2005; Rasmussen 2006).

This kind of intimate relationship between academic medicine and the drug industry was well established in Europe between the wars. As examples, the collaborations behind Schering's introduction of estrogens and IG Farben's introduction of sulfonamides can be cited (Gaudilliere 2005; Lesch 2006). Thus, it seems that by the 1930s, the US had largely caught up with the countries best exemplifying "scientific medicine", where pharmaceutical firms worked closely with preclinical and clinical leaders in academic medicine to develop new drugs. However, revealing a close relationship with drug firms could be detrimental to physicians' reputations; those who conducted studies funded

and possibly controlled by drug firms typically only acknowledged the donation of drugs in their publications (Rasmussen 2005).

During this period, what we now recognize as key opinion leaders (KOL) emerged in both preclinical and clinical drug research (the term itself dates from the 1950s (Katz and Lazarsfeld 1955)). In clinical research, the KOL physician offered his help to a firm in finding and justifying uses of a drug, and could advocate on behalf of the products in both the medical literature and the popular media (Rasmussen 2005; Rasmussen 2006). The sponsoring drug firm offered a KOL physician an opportunity to enhance his status through research. Both parties benefitted from the new drug's perceived value and success.

The fourth period started during the Second World War and continued to the end of the 1950s. The government projects for military purposes strengthened links between academic institutions and industry, helping to propagate and normalize collaborative research contracts. For the US, pharmaceutical examples include research on blood substitutes, cortical steroids, and penicillin (Creager 1999; Neushul 1993; Quinn 2013; Rasmussen 2002). Also larger and more disciplined controlled trials emerged for testing some of these war-related therapeutics.

After the war, the US government dramatically increased its support for academic biomedical research, as federal funding for basic research became greater than industry funding (Strickland 1989). As a great deal of preclinical knowledge was being generated in the public domain, sponsorship of clinical researchers became a greater focus for industry. Drug industry power and its role in the initiation of trials, their design and publication increased and drug firms increasingly relied on commissioned clinical trials to meet pre-specified commercial goals.

When the FDA gained statutory authority to require premarket safety testing in 1938, it issued regulations that effectively defined which drugs could be sold on prescription only. After surviving a court challenge, the regulations were written into law in 1951 (Marks 1995). Prescription-only regulation made physicians more important marketing channels than before (Tomes 2005). For example, during the 1950s it became common for industry to organize research conferences where industry sponsored studies were presented, and subsequently industry-funded journal issues were disseminated with the marketing message from those conferences (Fine 1972; Greene 2005). In the mid-1950s, possibly reflecting the new embrace of the mainstream medical profession and the drug industry, the AMA Council on Drugs ceased evaluating therapeutic claims. Gradually the FDA began to require the type of evidence the Council had required, but it did so on shaky legal authority (Carpenter 2010).

With the exploding number of new drugs in the 1950s there was a greater need for continuing medical education (CME) and no public actor to take on the task of funding this education. The drug industry took the central role in physicians' postgraduate and continuing education on therapeutics (Greene 2005; Greene and Podolsky 2009). The slogan "Selling drugs by educating physicians" (May 1961) shows that industry's motivation for sponsoring CME was recognized as other than altruistic by the early 1960s.

The drug industry and the clinical community had a mutual interest, both fearing increasing government involvement and control over medical research and practice as well as drug production and marketing. Particularly in the late 1940s and early 1950s, this was a sensitive political issue linked to the anti-communist sentiment of the time. The AMA mounted a campaign against the government

initiatives on national health insurance and other health reforms, defining them as "socialized medicine" (Poen 1979). To avoid dependence on government, medical schools solicited increased support for medical education from drug firms. These developments led to closer physician-industry relationships (Tobbell 2008).

The fifth period of the 1960s and 1970s started in 1962, when the thalidomide tragedy, during the Kefauver hearings on drug pricing, led to passage of the 1962 Kefauver-Harris amendments. These amendments gave the FDA the statutory authority to judge, not only the safety, but also the efficacy of experimental drugs on the basis of "adequate and well-controlled" trials before they could be marketed (Daemmrich 2004). At the same time, the FDA established Phases I-III premarket testing and began imposing more stringent trial design, making double-blind randomized controlled trials standard (Carpenter 2010). In essence, FDA took on the old role of the lapsed AMA Council on Drugs, but systematized it and gave it force of law. The US thus transferred the authority to judge the value of drugs from the medical profession to the government.

There were unsuccessful attempts to bring drug use under further federal control, such as requiring generic prescribing and putting the federal government in charge of testing new drugs. The proposal to tighten federal control of the practice medicine and drugs created a common enemy for industry and physicians, this time also including practicing physicians as well as researchers (Tobbell 2008; Greene 2014). The lack of FDA resources contributed to the creation of physician-industry expert advisory boards to advise the government on pharmaceutical research. They worked until 1975, and were first paid by industry (e.g., Drug Research Board) and later worked under the auspices of the National Academy of Sciences (Tobbell 2008).

Case of Finland

The information about the Finnish context comes from earlier Nordic research on drug control (Bruun 1983; Bruun 1982; Hemminki and Falkum 1980) and individual case studies (Hemminki 1980; Hemminki and Falkum 1980; Hemminki and McPherson 2000; Ollila and Hemminki 1996, 1997; Takala and Konstari 1982; Hemminki and Pesonen 1977). The development of the physician-industry relationship in Finland until the Second World War was different from that in the US. Both the general economic situation, organization of health care, drug production and distribution factors contributed to the difference. Unlike the US, a large number of poorly trained physicians was not a problem in Finland in the early 1900s. There were only a few physicians, but they were well trained, by the standards of that time. The creation of modern health services was a societal project and the state and municipalities were given the task of organizing health care. Pharmacies stayed outside the public system, but their contributions to it were regulated.

Pharmacists were important actors in drug policy and the drug industry was not an important factor in Finland until the 1930s. In Finland, like in the other Nordic countries, pharmacists were given the exclusive rights over medicine production and distribution in the 17th century. Well into the interwar period, pharmacists (including those who manufactured drugs) took the leading role in protecting the public against useless drugs, whereas in the United States this role had been taken up a by reforming medical profession. A key control principle in the 19th century legislation was to separate the functions of a pharmacist (to sell drugs) from that of a physician (to prescribe them). The aim was to remove the influence of monetary gain from prescribing. As far as we can judge from available documents, pharmacists did not try to influence physicians' practices, although in small communities the close social circles were likely to create "brotherhood networks".

Before the state assumed authority over drugs in the early 1960s, control was exercised by pharmacists, not physicians as in the US. Pharmacists used various tactics to keep their sales monopoly within pharmacies, including challenging the right of chemist shops to sell drugs (chemist shops were unregulated shops selling various products, including health related products), checking the quality of industry made drugs and later actively working for the state licensing of industry made drugs. As drugs went from being compounded inside pharmacies to being manufactured outside them, pharmacists turned from medicine makers into medicine distributors.

Drug firms. Even though foreign drug firms started selling drugs ("patent" medicines) in Finland towards the end of the 19th century, their position remained weak in the first third of the 1900s. A likely reason for their weak position was, besides the active campaign by professional pharmacists, the level of poverty in the country. Most people lived in the remote countryside and their purchasing power was low.

In the 1920s and 1930s, a tactic pharmacists used to retain their position in drug services was to make their own drug production more commercial and centralized. Some of these activities resulted in domestic drug firms. These firms were established in university towns, and at least in the neighboring country of Sweden, scientific connections with the local university medical faculty were strong, although an analysis of whether the same was true in Finland is lacking.

During the same period, the creation of domestic firms was a national project. This project was colored by a language battle; it was a way to get the Finnish speaking majority to have more economic and political power over the ruling Swedish speaking minority. Finnish drug firms were created to serve

Finland, to improve Finns' health and the Finnish economy. The state considered it its duty to promote the use of domestic products. Medical experts were active in creating and advancing local drug firms and their research. Drug firms produced established drugs and did not look for international markets and virtually no therapeutic innovation took place. As Finland had process patents rather than product patents, alternative ways of producing a drug as well as finding better administration methods were part of basic research. Clinical research consisted of the testing of local products.

After the Second World War the scene changed. The drug industry in Finland was no longer local, but subsidiaries of large international firms, which were not a part of the national project, established themselves in Finland. New powerful drugs were introduced and commercial marketing expanded.

Physicians. The Finnish Medical Association never took on the kind of control and education functions over drugs as the AMA did from 1905 to the 1950s. At the same time, in an atmosphere of working for the "common good", the connections between leading physicians and the local drug industry became close and accepted. In a parliamentary debate in 1934 on the problem of physicians owning drug company shares, the right was defended on the grounds that it was unfair to prevent physicians from having shares in drug firms "considering the service the medical profession had rendered the nation in helping to build up Finnish drug industry". The Ministry of Home Affairs said that "the intimate relationship between the medical profession and our industry is of course an enormous prop to our domestic products." (Bruun 1983).

Even though international drug companies were not a part of the national project, the drug firm-physician relationship largely continued as before. It seems that physicians' attitudes and values towards the drug industry continued to reflect those from the national project stage. The discussion of

potential problems resulting from the collaboration between the drug industry and physicians started later than in the US. The connections between physicians and industry and resulting problems were acknowledged, but they were thought to be minor compared to the benefits. The necessity of the close collaboration was defended by the small size of Finland. The defenders commonly used arguments about there not being enough experts to separate the academic/clinical and industry work.

A cross-sectional study on the connections between the leading physicians and the drug industry (Hemminki and Pesonen 1977) showed that leading physicians had multiple connections with industry and those with many key-roles had more connections. The paper resulted in no discussion or comments in Finland. But a year later, when one of the researchers applied for an academic position, a referee (the head of the National Board, the highest Finnish health authority) very critically commented at length on the paper and used it to argue against the applicant claiming that it showed "a sign of lack of scientific thinking".

Government. In Finland control measures regarding drugs were often weaker than in the neighboring Scandinavian countries. For example, drug licensing was introduced only in 1964 after the international pressure created by the thalidomide case. An issue that apparently contributed to the 1964 licensing law was the worry about the widespread use of dependence producing drugs. Unlike the US, the Finnish licensing law did not require that all available studies needed to be included in the application to market a new product. Drug licensing requirements included stipulations regarding marketing, but marketing was defined narrowly as advertising, i.e., advertising should not mislead physicians.

Government involvement in health care was better accepted in Finland than in the US. Health care was largely organized by public actors and there was no widespread fear of “socialized medical care”. After

the Second World War there was, however, a heated political debate about nationalizing (socializing) pharmacies and the drug industry. The arguments also included topics such as the commercial bias in drug use. However, unlike Sweden and Norway, no big changes occurred in the positions of pharmacy or industry, although public hospitals were allowed to establish their own pharmacies.

Discussion

The purpose of this paper was to summarize and compare the development of the drug firm-physician relationship in medical drug research from the late 19th century to the 1970s in two very different countries, the US and Finland. Our review, based on previous research, shows changes, commonalities and differences over time and between the two countries. Many themes important today were already found in the time period under study.

In both countries, by the 1950s the collaboration between physician experts and the drug industry was close, even though the reasons for collaboration were partly different. We hypothesize that a factor influencing the drug firm-physician relationship in medical drug research is the perceived success of therapeutic innovations; as more effective medications were invented and marketed by industry, the more acceptable drug firm involvement in medicine and medical care became. Another likely factor was the rewards medical experts and the drug industry gained from their collaboration. In the early 20th century, US medical experts wanted to increase the scientific basis of medical knowledge and care, and subjecting drug research by industry to academic standards was a tool in achieving this goal. In Finland medical experts were active in creating and advancing local drug firms and their research in order to get much needed drugs to market.

We found less research on the relationship between ordinary practicing physicians and the drug industry, but at least since the 1930s their role seems to have been largely confined to being the targets for marketing. In the US, marketing control was first exercised by medical experts through the AMA, and only later by government. To our knowledge, physicians were not notably involved in a regulatory function in Finland. In both countries control focused on a narrow range of advertising activities, e.g., advertisements in medical journals rather than on the broader range of marketing activities including visits by sales representatives and the distribution of free samples.

The available historical literature concerning Germany, France, and the Britain, tends to fit with the US story particularly after the Second World War. In the first third of the 20th century such reform activities as seen in the US were not found in Germany, France or Britain, where neither the medical profession nor the drug industry had sunk to such low regard in the public eye.

In the inter-war period the intimate relationship between academic medicine and the drug industry was well established in Europe. By the 1930s, American industry-medicine relations had come to resemble those that prevailed in Germany and France prior to that time.(Gaudilliere 2005; Quirke 2008; Rasmussen 2004; Rasmussen 2005) In Britain, a committee was established by the public Medical Research Council to design and oversee trials of new drugs with high standards. But this committee did little work before the Second World War, suggesting that industry was mostly still organizing its own collaborations.(Bryder 2011) Thus it seems that, by the 1930s, there was a convergence of academic-industry relations in the major western drug-making countries.

During the Second World War in many combatant countries, government projects for military purposes strengthened links between academic institutions and industry, helping to propagate and normalize

collaborative research contracts (Creager 1999; Gaudilliere 2005; Lesch 2006; Rasmussen 2002). Government also became involved in organizing clinical trials of large size and stronger standards. After the War the international convergence of academic-industry relations accelerated, and the drug industry became more multinational. Furthermore, emulating the American example, France, Britain and other western governments greatly increased their support for pre-clinical research (Austoker and Bryder 1989; Gaudilliere 2002; Geiger 1993; Strickland 1989).

In the US, in practice, regulation of the value of drugs had shifted from the medical profession to the government in the 1950s and became stronger in 1962 after the thalidomide episode (Carpenter 2010). Similarly, also after the thalidomide episode, an increase in government oversight of drugs occurred in Western European countries, although not to the same extent (Daemmrich 2004).

Academic-government-industry relations reflect larger societal trends (e.g. Rasmussen 2004; Daemmrich 2004; Tobbell 2012). One such trend is the acceptance of government's role in health care and its regulation of the drug industry. In the US, government regulation came later than professional control and largely as a reaction to drug scandals such as the 1937 elixir of sulfanilamide and 1962 thalidomide tragedies (Carpenter 2010). Government was seen a threat to physicians' autonomy and their ability to serve their patients' interests (Tobbell 2012; Tobbell 2008). Once government strengthened its regulatory role, the drug industry and medical experts worked together against this common enemy to prevent any further erosion of their autonomy. In Finland, government involvement was better accepted; there was no widespread fear of "socialized medicine". It seems that today due to the escalating costs of health care, the need to control drug prices and prescribing is better accepted by society, even in the US. But the old theme of the negative impact of government involvement on the

success of research and consequent drug innovation is still raised by physicians, in support of industry (Greene 2014; Tobbell 2012).

Relationships between doctors and the drug industry are still extremely common (Campbell et al. 2007), often having a negative impact on prescribing (Spurling et al. 2010). An important route through which industry influence occurs is via the gift relationship (Cialdini 2001). Doctors often recognized that, in general, these interactions and the acceptance of gifts can affect behavior but overwhelming they believe that this only happens to other members of the profession and that they themselves are immune from being influenced (Choudhry, Stelfox, and Detsky 2002; Rutledge et al. 2003; Steinman, Shlipak, and McPhee 2001). These belief patterns are consistent with cognitive dissonance theory whereby the discomfort between what doctors do and what they believe has to be resolved (Chimonas, Brennan, and Rothman 2007; Sah and Fugh-Berman 2013).

It seems that a resurgence of industry influence on clinical testing began in the 1980s, with the emergence of neoliberalism throughout the West, together with its ideological elevation of private industry (Abraham and Lewis 2014). By the early 2000s, there were widespread worries about a perceived recent emergence of excessive corporate influence over academic medical research (Abraham and Lewis 2014; Angell 2004). Whether the funding disclosure requirements in medical journals and the 2005 decision of the International Committee of Medical Journal Editors to require trial registration as a prerequisite of publication indicate the beginning of a new period of reform (Chalmers, Glasziou, and Godlee 2013; Davidoff et al. 2001; DeAngelis et al. 2004) is an open question. Recently, there seems to be a significant counter reaction to further reform as exemplified by a series of three commissioned articles in the New England Journal of Medicine, arguably the premier

general medical journal in the world, that argued that conflict of interest regulation has been taken too far (Rosenbaum 2015b, c, a).

Conclusion

To alleviate the problems of close drug firm-physician relationship, various suggestions and corrective measures have been made. Here we discuss ways to break the bond that holds physicians and the industry together by looking at the conduct of clinical trials and important practical applications of research results through medical education and clinical practice guidelines. Some of the reforms that we present have already been covered in Lexchin (Lexchin 2011; 2012) and so we only cite additional work not covered in this publication.

An overriding issue is whether declaring financial conflicts of interest (COI) is sufficient to mitigate them. The arguments against just declaring COI relate to the incompleteness and inaccuracy of declarations (physicians differ in what they consider to be a conflict), the difficulty of recipients who are not experts in a particular field in identifying a biased opinion, and "sanitizing" a problematic situation (suggesting that no ill effects will follow from the disclosed relationship) (Brennan et al. 2006; Cain, Loewenstein, and Moore 2005).

Preclinical research is not, and possibly should not be regulated. If society wants a certain basic science area to be studied, this could be achieved by directing money to that type of research. To avoid commercial bias in clinical drug research, measures such as impartial checking of the evidence submitted by firms for drug licensing, requirements for data openness and transparency and publishing negative findings have been proposed. However, these measures do not address the major problem of

medical drug research being almost fully dependent on industry funding. Particularly prior to drug licensing most information comes from industry supported and controlled clinical trials. The situation has existed since about the 1930s and measures to alleviate the problem have been slow to develop.

The patent and other intellectual property rights (IRP) system distorts the direction of the development of new medicines. Under this system companies have a monopoly on their products for up to 20 years. Companies develop products, design trials and control the knowledge from those trials in order to generate the greatest amount of revenue possible. Rather than continuing to pay companies based on the price of their products and the amount sold, the new goal should be to pay companies based on the therapeutic value of their drugs. One approach to that is the Medical Innovation Prize Fund bill delinking the incentives for research from high drug prices through innovation inducement prizes proposed in the US (Love 2015). There are also other proposals aiming to reform the IRP system to support research priorities from a health perspective, without putting research funding at risk (Love 2015).

From a historical perspective it seems that one of the main factors bringing physicians and drug industry together was their joint desire to develop new drugs, albeit possibly for different reasons; in the case of physicians to treat their patients better and to be recognized for their expertise, and in the case of industry for commercial profit. We are not advocating that physicians should avoid doing clinical trials for industry. But we believe that a firewall must be established between them and the firms on how trials are designed, carried out and analyzed. This should be done to avoid biases introduced by the funding of the trials. A model suitable for some countries might be that drug firms would not directly compensate physicians or their institutions for evaluating company developed products, but physicians would work for the testing agency. In the US , the institution could be the

National Institutes of Health (NIH) (Lewis, Reichman, and So 2007). The NIH would receive the money necessary to conduct the trial and then select the researchers who would independently design, organize and manage clinical trials and the data that comes out of them, and write the results independent of the sponsoring company.

Physicians' exposure to drug industry starts in medical school (Austad, Avorn, and Kesselheim 2011; Mintzes 2005; Mintzes, Mangin, and Hayes 2010). Surveys of medical schools in Australia, Canada and the US show that COI policies are weak (Chimonas et al. 2011; Mason and Tattersal 2011; Shnier et al. 2013), although improving in the US (AMSA: American Medical Student Association 2012). Continuing medical education (CME) has become mandatory in many countries. In the US drug companies have been important supporters of CME (Steinman, Landefeld, and Baron 2012) and anecdotal observations suggest that it is also true in other countries.. We propose a full separation of academic medical education, including CME, from drug industry support. Medical schools should have much more restrictive policies in regard to commercial firms (Brennan et al. 2006), and gifts (including "no strings attached" grants) to individual researchers should be prohibited. Commercial money for CME should go to a central fund that would distribute the funding to accredited programs (Brennan et al. 2006). Some physician associations in the US have decided that they can forgo industry funding for CME events (Silverman 2008).

Clinical practice guidelines are increasingly influential in defining how physicians should practice (O'Malley, Pham, and Reschovsky 2007); they are a crucial part of physicians' continuing education. Often experts writing the guidelines have various drug and other industry affiliations and COI, distorting the message in the guidelines (Cosgrove et al. 2013; Norris et al. 2011). The recommendations for minimizing the effect of financial COI (fCOI) include: the chair and co-chair

should not have fCOI, the committee selection process should be stated, all committee members should declare their fCOI, the method of collecting the data should be clearly stated, the quality of the evidence should be clearly rated and the evidence supporting individual recommendations should be given (Graham, Mancher, and Wolman 2011). These standards offer a minimum starting point to reduce bias in guidelines.

The suggestions above could notably reduce biased information from influencing practicing physicians. They would not solve the commercial bias in medical knowledge, but they would be a beginning in helping physicians to treat their patients based on the most objective knowledge available.

Table 1. Comparison of different time periods in the US in regard to degree of commercial bias in drug research

Period	Trial methods	To avoid bias	Drug inventions	Standards for clinical testing	Industry role in clinical testing	publication control	Marketing control	Base for marketing to physicians
Circa 1900	historic controls	stratification	universities and similar	..	none	none	none	seeding trials, testimonials
1905-1930	systematic comparison	comparable groups, blinding	universities and similar	AMACD	AMACD advised industry	none	AMACD	testimonials, preclinical? and clinical research
1930s	systematic comparisons	comparable groups, blinding	jointly drug industry and universities	AMACD	commissioned trials	drug firms[1]	AMACD	testimonials, preclinical and clinical research
2nd WW-1950s	systematic comparisons, RCT introduced	comparable groups, blinding, randomization	jointly drug industry and universities	AMACD/ FDA (both weak)	commissioned trials	drug firms[1]	AMACD[2]	clinical research
1960s - 1970s	controlled trials	randomization, comparable groups, blinding	jointly drug industry and universities	FDA (statutory)	commissioned trials	drug firms[1]	FDA	clinical research

AMACD= American Medical Association Council on Drugs, FDA= Food and Drug Control, RCT = randomized controlled trial, WW= world war

[1] for commissioned studies

[2] closed mid 1950s

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