Linking Research and Marketing, a Pharmaceutical Innovation

Sergio Sismondo
Queen's University
Kingston, Canada K7L 3N6
sismondo@queensu.ca

Abstract: This chapter describes in very general terms the integration of clinical research and marketing, drawing on books by marketers and recent cases that have come to the public eye. The tools that have been used to accomplish this integration over the past half-century are various, but they all stem from a realization that in a rational world centered on health there need be no intrinsic divide between research and marketing. Most obviously, marketing drugs to physicians, who are professionals acting within their own spheres, depends crucially on research. Physicians respond, and need to see themselves as responding, to fact, figures, and studies. The well-chosen images and vehicles for marketing campaigns must be subordinated to research. Yet at the same time research is a means of increasing sales.

> In 1991, William C. Steere, Jr., the new CEO of Pfizer, started a re-organization of the company. "'He told me he had three priorities," recalls [Steve] Conafray [then head of political affairs at Pfizer] … "The first one was get marketing and research closer together. The second one was get marketing and research closer together. And then he said the third one was get marketing and research closer together.' Everyone got the message." (Critser 2005, 91)

Introduction: a phenomenon

Let us begin by looking at a recent drug, rofecoxib, vigorously marketed as Vioxx by Merck. Rofecoxib has attracted considerable media attention because in 2004 Merck voluntarily withdrew the drug, noting new evidence that its users faced

increased chances of cardiac arrest. That action prompted many lawsuits, some closer looks at the research on rofecoxib, and a claim that Merck may have inappropriately withheld data. This paper ignores these issues.[1] Instead, it draws attention to a way in which rofecoxib is a typical high-volume drug of its era, or at least was until it was withdrawn from the market. In particular, rofecoxib is not most importantly characterized by shortage of research on its defects, but by a super-abundance of research, mainly clinical research, on its benefits.

Rofecoxib is a COX-2 inhibitor. The discovery that acetylsalycilic acid (ASA) inhibits the cyclo-oxygenase (COX) enzymes that allow for the production of prostaglandins important to inflammation and pain (Piper & Vane, 1971) led to further research in this area. It was found that there are multiple isozymes — different, usually closely related, enzymes that catalyze the same reactions — of the cyclo-oxygenases. COX-1 produces constitutive prostaglandins, serving functions of protecting the gastrointestinal and renal tracts, as well as producing blood platelets. COX-2 produces prostaglandins induced by injury, and cause inflammation and pain. Traditional non steroidal anti-inflammatory drugs (NSAIDS) such as ASA act on both of these systems, effectively reducing pain and inflammation, but leading to increased chance of gastrointestinal damage and to decreased platelet production (advantageous to those at risk of cardiovascular problems). COX-2 inhibitors should reduce pain and inflammation, but with fewer effects on gastrointestinal systems.

Rofecoxib was approved by the U.S. Food and Drug Administration (FDA) in 1999, for relief of osteoarthritis, acute pain, menstrual pain; approval by other

national regulatory bodies followed. It was the second COX-2 inhibitor approved by the FDA, after Pfizer's (then Pharmacia's, before subsequent mergers) celecoxib (Celebrex) in 1998. Efforts to create large markets, and competition between the two — and a further Pfizer COX-2 inhibitor, valdecoxib (Bextra) — led to substantial advertising and marketing campaigns. Both rofecoxib and celecoxib were "blockbuster" drugs by 2001, boasting $2.6 billion and $3.1 billion in sales respectively that year. Blockbuster drugs are usually defined as ones with sales of more than US $1 billion per year, and in recent years the pharmaceutical industry has been dominated by attempts to create blockbusters; they will likely remain important despite pressures to create more "niche" drugs (e.g. Carpenter 2006).

A Medline search (performed in March, 2006) for the keyword "rofecoxib" pulls up 1560 articles published between 1999 (i.e. the year the drug was first approved) and 2003, and a search for the keyword "celecoxib" pulls up 1872 in that same period. Restricting those searches to "core clinical journals" reveals 161 articles on rofecoxib and 196 on celecoxib; core clinical journals are approximately 130 journals chosen for the Abridged Index Medicus, on the basis of their importance and because they publish articles on clinical research of wide interest, either generally or within major specialties (Abridged Index Medicus 2006). Though many of the articles turned up by that search are other types of systematic articles, such as reviews or reports of meta-analyses, the majority of them are reporting on clinical trials involving these drugs. And almost all of the articles are centrally *about* these drugs, perhaps among others, in some

important sense.

Here we have an interesting phenomenon: blockbuster drugs are blockbuster research targets! The phenomenon is not limited to COX-2 inhibitors, but can be as easily seen among other classes of drugs. For example, a keyword search on the cholesterol-lowering agent atorvastatin (Lipitor) brought up 512 articles in core clinical journals in a similar period, and the proton-pump inhibitor for acid-related gastrointestinal problems omeprazole (Losec, Prilosec, Nexium) had 1155 articles in core clinical journals in a similar period. New drugs that are "orphans," for which there are few potential patients, are associated with small or only modest amounts of published research.

Thus there is a fairly good correlation between the number of clinical research articles published in medical journals and the market status of a drug. The rest of this paper discusses some of the possible reasons for that correlation.

Large potential markets beget research

This phenomenon has existed for at least thirty years, though it may be not much older than that. Taking the period 1975 to 1979 as a comparison, there were approximately 100 articles in core clinical journals on each of a number of well-prescribed drugs, such as ibuprofen (then Brufen or Motrin), represented by 83 articles, though there are a few very prominent drugs featured in considerably more articles: diazepam (Valium) sees 400 articles in core clinical journals, and for methylprednisolone (Medrol) there are 313.

There are obvious structural reasons why there should be some correlation

between number of articles published and market status. Clinical researchers want to do research, and it is much easier to do a study of a drug for which there are many potential consumers than for which there are few. Thus it is, perhaps, unsurprising that there would be few studies of genuine "orphan" drugs: such studies are very difficult to run, as it is difficult to recruit patients. But while bottlenecks because of small numbers of patients might explain cases in which there are few studies, they do little to explain much of the rest of the variation.

Between 1999 and 2003 there were only three articles in core clinical journals on the new drug cevimeline, used to treat Sjögren's syndrome, an auto-immune disease with an incidence rate of between one-third and one percent of the population of Western countries (NIH estimate, at CureResearch.com 2006). Compare these numbers with the 1155 articles on omeprazole, indicated for the gastroesophageal reflux disease (GERD), affecting an estimated three percent of Western populations — though many more people are affected by conditions that are potential precursors to GERD, such as frequent heartburn (NIH estimate, at CureResearch.com 2006). The major difference between these two pairs of drugs/illnesses is not the difference between the number of potential patients with Sjögren's syndrome and the number of potential patients with GERD, but that omeprazole has become very widely prescribed, especially in the United States, for heartburn and other problems involving excess stomach acid. This wide usage is a *result* of marketing by AstraZeneca (and earlier marketing by Glaxo of Zantac for GERD); AstraZeneca's direct-to-consumer advertising for the "purple pill" has taken on an iconic status, commonly cited by both marketers

and critics as among the most aggressive and successful campaigns for any drug (e.g. Schmidt 2004). Meanwhile, clinical research on omeprazole is presumably not driven by an intrinsic medical interest in heartburn. We gain a coherent picture if we see both the number of prescriptions and the number of articles as driven by efforts to fill the largest potential market. This phenomenon is particularly well studied in the area of psychopharmacology, where work by such researchers as David Healy (2003, 2004) and Charles Medawar and Anita Hardon (2004), has established that the growth of interest in depression and other recently important psychiatric conditions has been fueled by the promotional work of pharmaceutical companies. But the phenomenon is widespread: Returning to the case of rofecoxib, large numbers of articles were being published at the same time that Merck was heavily advertising Vioxx, creating the potential for it to be seen as a general painkiller, rather than simply a drug for managing osteoarthritis. At least some of the time, then, important drugs and conditions become important because commercial interests support them.

PhRMA, the pharmaceutical industry lobbying agency in the United States, claims that its members spent US$39 billion (thousand million) on research and development in 2005 (PhRMA 2006), the vast majority of which was spent on clinical trials. The entire budget of the National Institutes of Health in that year was US$28 billion, some of which was spent on research unrelated to pharmaceuticals, and much of which was spent on research other than clinical trials. The pharmaceutical industry therefore provides a very high percentage of the support for clinical trials in the United States, and probably the majority of

that support. Consequently, the industry has the means to have considerable influence on which drugs and conditions are worth studying.

Articles are marketing tools

> According to a study recently commissioned by the *New England Journal of Medicine*, physicians view reprints from NEJM as qualitatively superior to those from similar journals. The survey, conducted by the Matalia Group, queried 3,400 physicians and residents in cardiology, family practice, hematology/oncology, infectious diseases, internal medicine and oncology. The study concluded the following:
>
> •Next to peer-reviewed journals, reprints are the most reliable information source for physicians.
> •NEJM reprints influence physicians' behavior.
> •In most specialties surveyed, physicians recall receiving more reprints from NEJM than any other journal.
> •NEJM reprints are considered significantly more relevant and valuable to physicians' practices than reprints from other journals.
>
> (Massachusetts Medical Society 2003)

As the above notice in the Massachusetts Medical Society's "Vital Signs" indicates, reprints of medical articles are valued for their ability to influence physicians' behavior. The notice is effectively an advertisement for a product sold by Massachusetts Medical Society, reprints from its publication, the *New England Journal of Medicine*. Pharmaceutical companies and their agents are the largest buyers of reprints, buying them in numbers ranging from the large to the very large. Richard Smith, a former editor at the *British Medical Journal*, reports that pharmaceutical companies can spend more than a million dollars on reprints of a single article (Smith 2005). Even if that figure represents an exceptional case — it suggests a print run in the hundreds of thousands — it remains that NEJM can quote standard prices on orders of 10,000 reprints of an eight page article in black and white (US$15,974, quote emailed to author). Most other medical

journals also sell reprints, and their publishers advertise them, and associated services, to pharmaceutical companies. Blackwell, for example, claims to be able to deliver reprints within ten working days of an order, and to be able to add company logos, advertisements, or product information (Blackwell 2006).

Reprints are deployed by drug representatives in their visits to physicians, or, as a last resort, are mailed to physicians as part of marketing campaigns. They provide the scientific evidence to back up drug representatives' and advertisers' claims. When holding a reprint of a scientific article, drug representatives stand simultaneously as promoters of products and as communicators of scientific information. Reprints thus facilitate companies' claims to be part of an "ethical pharmaceutical industry" distinguished from the patent medicine companies of an earlier age, and their descendants, still ably competing today.

There are 90,000 drug representatives (officially "pharmaceutical sales representatives") in the United States (Elliott 2006), with a population of approximately 700,000 active physicians (U.S. Census Bureau). Earlier labels, "detail men" or "detailers," suggested the scientific role drug representatives were supposed to play: as communicators of detailed information, as translators of medical research into terms ordinary physicians can understand. They do much more than that, of course: they are best known for dispensing free samples, for taking physicians and their staff to lunch, and for leaving well-chosen reminders — from pens with logos to fine wines — of them and their products. Because doctors generally do not want to see themselves as influenced

by mere gifts or advertising pitches, the scientific information is particularly important. Thus already in the 1950s handbooks for detailers established rules of behavior that placed them as scientific colleagues of doctors (Greene 2004).

As has been noted many times, the randomized, controlled trial (RCT) is relatively new to medicine. Although one can find a number of fore-runners, credit for the first RCT in medicine is often given to Austin Bradford Hill, for his 1946 trial of the effect of streptomycin on tuberculosis, and for his advocacy of RCTs in medicine (Timmermans & Berg 2003, Marks 1997). The rise of the RCT over the following few decades, to become the "gold standard" of clinical research by the 1990s, followed such events as the birth defects caused by thalidomide (Timmermans & Berg 2003) and extensive advocacy by statisticians and statistically-minded medical researchers (Marks 1997). Since the 1970s, physicians have been repeatedly told that they should pay attention to only kind of reliable information, reports of randomized, controlled trials (e.g. Sacks et al, 1982). Other forms of information, to the extent that they are reliable, are built on top of those RCTs: meta-analyses and review articles are analyses of RCTs.

The intersection of research and marketing, then, is dominated by the intersection of randomized controlled trials and marketing. If pharmaceutical companies are to approach physicians to convince them of the merits of their products, they are almost forced do so using the results of RCTs. Physicians — not to mention most other people who buy or control the buying of drugs — want their drugs to be part of a rational world centered on health. Any visible aspect of drug research, development, or promotion that is not part of a logic of health is

immediately suspect. Thus pharmaceutical companies have a strong incentive to ensure that there is useful clinical research on products they wish to sell widely.

It is not merely that pharmaceutical companies support research for independent reasons, and reap the benefits of having articles for their representatives to deploy and opinion leaders who support their interests. The companies recognize the value of research, and support it for that value. In the early 1990s, Pfizer wanted to sell its selective serotonin reuptake inhibitor (SSRI) sertraline (Zoloft) in a market dominated by fluoxetine (Prozac) and a few other early SSRIs. To catch up with the competition, Pfizer applied its CRAM ("Central Research Assists Marketing") program to the problem. The company commissioned research to show that sertraline had a cleaner breakdown route, and was associated with higher quality of life, than its competitors (Healy 2003; Critser 2005). The data could then be used at seminars, sales events, and continuing medical education to mark distinctions between sertraline and other SSRIs. Meanwhile, Pfizer created programs to educate physicians about depression, which could be expected both to increase the number of diagnoses of depression and the number of prescriptions for that product: Unbranded disease awareness campaigns have substantial effects on sales of particular brands, perhaps because of consilience between unbranded and branded information ('t Jong et al. 2004).

Opinion leaders and the use of research

Medical journal articles themselves, even without being reprinted, even without

being transported to doctors' offices, must have some marketing value. This value of research in isolation is limited, given the few physicians who have the time or inclination to read widely in medical journals. But presumably a significant bulk of publication will have some effect, if it conveys a sense that a drug is attracting attention and being taken seriously by the research community. And if articles are read and assimilated by "opinion leaders" — who may serve as consultants on research, as members of speakers bureaus, or as educators — and then translated into forms by which their conclusions reach more prescribers, then their value as marketing tools increases. Of course if articles are read and translated by journalists, their value is even higher.

Influencing opinion leaders is a key part of many promotional campaigns. An advertisement for a report (*Pharmaceutical Thought Leaders*, priced at US $6995) by the research firm Cutting Edge Information, says:

> The most lucrative thought leader relationships are steeped in cutting edge scientific research that helps the company promote its treatments while allowing the physician to advance her interest — and influence — in a given area. (Cutting Edge Information 2004)

Opinion leaders are courted starting as early as Phase I research does, and by one estimate pharmaceutical firms spend an average of US $40 million per brand supporting opinion leaders (Cutting Edge Information 2004). Expenses come in such varied forms that firms may not know how much they are paying even individual opinion leaders: an article in *Pharmaceutical Executive* worries that not knowing how much is being paid to individual opinion leaders could result in public relations disasters (Chaudhry & Love 2005). The problem is a difficult one because "the number of physicians available to play these roles cannot keep

pace with demand," and as a result individuals play many roles, from clinical trial investigator to expert speaker to advisory board member (Chaudhry & Love 2005). The language of supply and demand suggests opinion leaders' status as resources.

Opinion leaders are not given only monetary reward. They are given status, or support for status, by being given forums. In some of their roles opinion leaders are given research support, allowing them to conduct the research that leads to published articles. They may also be given access to valuable data, collected in studies in which they may or may not have participated. They may even be given direct access to publication in the form of ghost-authoring. One study of authorship for major medical journals found that 11% of articles show evidence of having ghostwriters, and 19% of having honorary authors (Flanagin et al. 1998). In extreme cases, drug companies pay for research by contract research organizations, have ghostwriters put together manuscripts, and then give those manuscripts to academic researchers who have had no prior connection to the research (Barnett 2003, Healy 2003, Johnson 2003). Those honorary authors append their names to the tops of the articles, simultaneously sponsoring the research and padding their publication records. They stand as guarantors of quality, even though they may have had little or no control over the claims that are made under their names. Pharmaceutical companies and their agents support ghost-authoring because of the value of independent research — and in the support of ghost-authoring we can again see that the companies *recognize* the marketing value of research.

Active researchers are intermediaries

Pharmaceutical companies operate in many arenas at once: medical, research, educational, financial, regulatory, and legal. To a greater or lesser extent, the expertise of academic medical researchers is relevant to all of these arenas. Thus the companies cultivate researchers whose views support their interests, and cultivate views that support for their interests among researchers.

It is well established that there are associations between research funding and research results, and evidence that those associations can be extended to views as well. In a review of studies on the relations of support and results, Joel Lexchin and co-workers (Lexchin et al 2003), show that industry-funded clinical studies report positive results more heavily than non-industry-funded studies, with an odds ratio of 4.05. An observation from the regulatory debates around COX-2 inhibitors suggests an extension of such results. After Merck's voluntary withdrawal of rofecoxib, and evidence showing that a Pfizer COX-2 inhibitor, valdecoxib (trade name Bextra) also increased heart risks, an FDA advisory committee made recommendations about the three COX-2 inhibitors that had been approved. On that committee 10 members had declared conflicts of interest because of financial associations with Merck and Pfizer. Those 10 members voted 9 to 1 in favor of keeping valdecoxib on the market, and 9 to 1 in favor of bringing rofecoxib back on the market. The other members voted 12 to 8 against and 14 to 8 against on the two issues (Harris & Berenson 2005). Thus there was in this case a very high correlation between association with the industry and

votes in its favor, suggesting that these experts with industry associations were, probably without recognizing it, serving as pharmaceutical companies' representatives in FDA meetings (see also Lurie et al. 2006 for a consistent but less dramatic analysis of FDA advisors more generally).

Jennifer Fishman (2004) describes how researchers on female sexual dysfunction acted as mediators between pharmaceutical companies, the FDA, physicians, and potential consumers. For example, in 2001, researchers organized a consensus conference on "Androgen Deficiency in Women," designed to establish the definition of and diagnostic criteria for this developing disorder. The conference was supported by grants from several pharmaceutical companies in the process of developing testosterone products for women, and was important to the prospects for success of these products, because the FDA only approves drugs that treat established medical disorders. The conference's consensus document, then, was a key step in establishing the regulatory legitimacy of female sexual dysfunction in the form of "female androgen insufficiency syndrome" (Fishman 2004, 193). In addition to looking at documents, the FDA turns to researchers like the conference organizers and participants in order to judge the documents: they have the relevant expertise to contribute to the agency's decisions. It is telling that the FDA was represented at the conference, giving a presentation on preferred endpoints of trials.

Published research, continuing medical education, and opinion leaders are all useful for expanding markets, either via "disease mongering" (e.g. Moynihan & Henry 2006) or the promotion of "off-label uses". Disease mongering, as in the

case of female sexual dysfunction (see also Tiefer 2006), requires not only academic and regulatory recognition of medical conditions, but also physician and patient recognition of those conditions. Academics thus also serve as mediators between pharmaceutical companies and practicing physicians. The conference Fishman uses as an example included a Continuing Medical Education (CME) component for local physicians. While they earned CME credits, they learned about products they could prescribe off-label for women's complaints about low sexual desire. This is not unusual in CMEs: in 2001 the pharmaceutical industry claimed to provide funding for half of all CME courses in the U.S. (Holmer 2001).

Doctors may prescribe a drug for whatever condition they think it warranted, even while regulatory agencies only approve drugs for particular uses. Prescriptions for unapproved uses, which are common, are off-label, and may form an important part of the market for a drug. Because off-label promotion by drug companies is illegal, research, education, and word of mouth — through published articles, CME, and opinion leaders — are vectors by which information about alternative uses of drugs can be disseminated. In a suit challenging Parke-Davis's marketing of Neurontin, an executive was found to have said to marketing managers:

> Dinner programs, CME programs, consultantships, all work great, but don't forget the one-on-one. That's where we need to be, holding their hand and whispering in their ear, Neurontin for pain, Neurontin for monotherapy, Neurontin for bipolar, Neurontin for everything. (quoted in Critser 2005, 105-6)

Academics who jump early onto developing disorders, then, receive research support, attention from their colleagues and the media, and have

significant influence on the shape of regulatory and medical decisions — on the shape of medical disorders.

Pharmaceutical companies also support research by non-academic physicians, who serve as intermediaries in so doing. What is called "postmarketing research" is done after approval by regulatory agencies. While the term has wide use, it is commonly applied to studies designed to familiarize physicians with products, to encourage prescriptions, or to allow drug representatives more access to prescribers. "Seeding trials" pay physicians to prescribe specific drugs as part of trials, but are clearly aimed at increasing prescriptions. A U.S. Federal investigation revealed that in some of Schering-Plough's post-marketing trials of its hepatitis C treatment Intron A, liver specialists were paid between US$1000 and $1500 per patient enrolled in the trials (Harris 2004). There were, doctors claimed, few efforts to ensure that doctors would collect and forward data to the company. Such a trial can be a successful seeding trial because the Intron A was not provided for free, as it would be in a Phase III trial, but was paid for by patients and their insurers, at an annual cost of more than $20,000 (when packaged with Schering-Plough's ribavarin). The physicians who participate may gain status, as well as money, by becoming researchers and not merely prescribers. They may give, and not only receive, continuing medical education.

For the purposes of this chapter, what is relevant about postmarketing research is that it is research, and at least sometimes is published. It thus provides a route via which promotion efforts turn into academic articles,

contributing to the large numbers of articles on commercially important drugs.

Conclusion

Clinical research on pharmaceuticals, then, is not merely research. It serves a number of functions at once, only some of which are importantly related to increasing the knowledge held by the medical research community. The pharmaceutical industry needs to be able to display scientific research when it markets its products, in order to be part of scientific medicine. It needs to support researchers, who can then act as intermediaries between it and various key groups and agencies. It uses studies as tools for encouraging prescriptions of its products, and as tools for gaining influence with researchers and physicians. And it has the resources to encourage the development of research areas and literatures. The phenomenon with which we started, then, large numbers of journal articles about particular commercially-important products, is exactly what we should expect to see given this constellation of pressures.[2]

Works Cited

Abridged Index Medicus. 2006. Abridged Index Medicus (AIM) Journal Titles. http://www.nlm.nih.gov/bsd/aim.html (accessed October 5, 2006).

Barnett, Antony. 2003. "Revealed: how drug firms 'hoodwink' medical journals." *The Observer*. Sunday, December 7. http://observer.guardian.co.uk/uk_news/story/0,6903,1101680,00.html (accessed August 16, 2004).

Blackwell. 2006. Advertisement for Blackwell Reprints. http://www.blackwellpublishing.com/MedStudent/healthcare/reprints.asp (accessed April 1, 2006)

Carpenter, Gareth. 2006. "The Notable Marks." *Pharmaceutical Marketing,* Sept. 6, 2006. http://www.pmlive.com/

Chaudhry, Kashif & Anne Love. 2005 "Key Opinion Leaders Interactions with Pharma." *Pharmaceutical Executive*, October 1, 2005. http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=197784&pageID=1 (accessed April 1, 2006).

Critser, Greg. 2005. *Generation Rx: How Prescription Drugs Are Altering American Lives, Minds, and Bodies*. New York: Houghton Mifflin.

CureResearch.com. 2006. "Conditions by People Affected." http://www.cureresearch.com/lists/preval.htm (accessed April 1, 2006)

Cutting Edge Information. 2004. Advertisement for *Pharmaceutical Thought Leaders: Brand Strategies and Product Positioning*. http://www.pharmathoughtleaders.com/index.htm#body (accessed April 1, 2006)

Elliott, Carl. 2006. The Drug Pushers. *The Atlantic Monthly*, April 2006: 82-93.

Fishman, Jennifer. 2004. "Manufacturing Desire: The Commodification of Female Sexual Dysfunction." *Social Studies of Science* 34: 187-218.

Flanagin, Annette, Lisa A. Carey, Phil B. Fontanarosa, Stephanie G. Phillips, Brian P. Pace, George D. Lundberg, Drummond Rennie. 1998. "Prevalence of Articles with Honorary Authors and Ghost Authors in Peer-Reviewed Medical Journals." *Journal of the American Medical Association* 280 (3): 222-224.

Greene, Jeremy. 2004. "Attention to 'Details': Etiquette and the Pharmaceutical Salesman in Postwar America." *Social Studies of Science* 34: 271-292.

Harris, Gardiner. 2004. "Medical Marketing — Treatment by Incentive; As Doctor Writes Prescription, Drug Company Writes a Check." *New York Times*, June 27, 2004.

Harris, Gardiner & Alex Berenson. 2005. "10 Voters on Panel Backing Pain Pills Had Industry Ties." *New York Times* (electronic edition), February 25, 2005.

Healy, David. 2003. *Let them Eat Prozac*. Toronto: James Lorimer.

Healy, David. 2004. "Shaping the Intimate: Influences on the Experience of Everyday Nerves." *Social Studies of Science* 34: 219-246.

Holmer, Alan F. 2001. "Industry Strongly Supports Continuing Education." *Journal of the American Medical Association* 285 (April 18): 2012.

't Jong, Geert.W., Bruno H.Ch. Stricker, and Miriam C.J.M. Sturkenboom. 2004. "Marketing in the Lay Media and Prescriptions of Terbinafine in Primary Care: Dutch Cohort Study." *British Medical Journal* 328: 931.

Lexchin, Joel, Lisa A. Bero, Benjamin Djulbegovic, and Otavio Clark. 2003. Pharmaceutical Industry Sponsorship and Research Outcome and Quality: A Systematic Review." *British Medical Journal* 326: 1167-70.

Lurie, Peter, Cristina Almeida, Nicholas Stine, Alexander R. Stine, Sidney M. Wolfe. 2006. "Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings." *Journal of the American Medical Association* 295: 1921-1928.

Marks, Harry. 1997. *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990*. Cambridge: Cambridge University Press.

Massachusetts Medical Society. 2003. "Reprints Study Shows Value of New England Journal of Medicine Content." http://www.massmed.org/Content/NavigationMenu3/BackIssues/2003/May2003/InsideMMS/Reprints_Study_Show.htm (accessed April 1, 2006).

Medawar, Charles and Anita Hardon. 2004. *Medicines out of Control? Antidepressants and the Conspiracy of Goodwill*. Amsterdam: Aksant Academic Publishers.

Moynihan, Ray, and David Henry. 2006. "The Fight against Disease Mongering: Generating Knowledge for Action." *PLoS Medicine* 3 (4): e191.

PhRMA. 2006. "R&D Investments by America's Pharmaceutical Research Companies Near Record $40 Billion in 2005." http://www.phrma.org/

(accessed May 5, 2006)

Piper, P, and J Vane. 1971. "Release of Prostaglandins from Lund and other Tissues." *Annals of the New York Academy of Sciences* 180: 363-

Sacks, Henry, Thomas C. Chalmers, and Harry Smith, Jr. 1982. "Randomized versus Historical Controls for Clinical Trials." *The American Journal of Medicine* 72: 233-240.

Schmidt, Charles W. 2004. "Matters of Money." *Modern Drug Discovery* 7 (March 2003). http://pubs.acs.org/journals/mdd/index.html (accessed October 5, 2006)

Smith, Richard. 2005. "Medical Journals Are an Extension of the Marketing arm of Pharmaceutical Companies." *PLoS Medicine* 2 (5): e138.

Tiefer, Leonore. 2006. "Female Sexual Dysfunction: A Case Study of Disease Mongering and Activist Resistance." *PLoS Medicine* 3 (4): e178.

Timmermans, Stefan, and Marc Berg. 2003. *The Gold Standard: The Challenge of Evidence-Based Medicine and Standardization in Health Care*. Philadelphia: Temple University Press.

U.S. Census Bureau. 2006. http://www.census.gov/ (accessed May 2, 2006).

---

[1]This paper is part of a larger research project on research and marketing. In other parts of this project I explore these problematic issues about rofecoxib.

[2]I would like to thank Viviane Quirke and Judy Slinn for very helpful comments and criticisms of an earlier draft. The writing of this paper was supported by a grant from the Social Sciences and Humanities Research Council of Canada.