

Ethical Transparency and Government Regulation of Canada's Medical Research Industry

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Medical research and development (R&D) is an area where the interests of private sector firms often conflict with those of governments.¹ More precisely, the private sector firms conducting the bulk of medical R&D are motivated by the ethical standards of the marketplace.² These standards differ from those of government which, in Canada, is an advocate for patients as well as having monopoly control of the health care system through the publicly-funded, provincially-run Medicare and Pharmacare systems. In this environment, there is a strong incentive for government to require a high level of ethical transparency in the regulatory filings that firms conducting medical research are required to provide. However, at least since Nancy Olivieri versus Apotex, there has been accumulating evidence that current levels of disclosure still do not make it possible to separate legitimate medical research from a corporate strategy of marketing patent protected medical products to physicians.³ This paper will examine the economic medicalization of medical research practice and publication in Canada. The discussion is used to motivate a more general examination of the problems involved in the ethical approval process for medical research that balances the interests of both business and government in the Canadian medical arena.

I. The Medicalization of Society

Medicalization is a social process where the medical profession extends its authority over matters not directly concerned with the analysis and treatment of biophysical disorders. In this definition, the medical profession includes not only practising doctors and associations of doctors but also: the pharmaceutical industry, providing the drugs that are an essential component of modern medicine; the academic institutions and journals involved in training doctors and sponsoring essential research activities; and, the government granting agencies and other sponsors that supply essential funding to the research conducted by the medical

¹ C. Robbins-Roth (2000), *From alchemy to IPO : the business of biotechnology*, Cambridge, MA: Perseus; M. Angell (2004), *The Truth About Drug Companies: How They Deceive Us and What To Do About It*, New York: Random House; R. Moynihan and A. Cassels (2005), *Selling sickness : how the world's biggest pharmaceutical companies are turning us all into patients*, Vancouver: Greystone Books.

² G. Poitras (1994), "Shareholder Wealth Maximization, Business Ethics and Social Responsibility" *Journal of Business Ethics*. 13:125-34.

³ J. Thompson, P. Baird and J. Downie (2001), *The Olivieri report : the complete text of the report of the independent inquiry commissioned by the Canadian Association of University Teachers*, Toronto : J. Lorimer; S. Sismondo, S. (2004), "Pharmaceutical Maneuvers", *Social Studies of Science* 34:149-159; M. Lynch, M. (2004), "Ghost Writing and Other Matters", *Social Studies of Science* 34: 147-148.

profession.⁴ Significantly, because the source of capital for the pharmaceutical industry is the global financial markets, the primary motivations of this important player in the medical profession differ from those of the other players. The implications of this difference are the substance for a legion of studies on the marketing networks of the pharmaceutical companies and the sophisticated efforts involved in selling products. The differing motivations within the medical profession create an ethical dilemma for government regulators: how to balance public health concerns with the need to restrict the economic footprint of the regulatory framework on an industry that produces and distributes some of the most important products of modern science?

The concept of medicalization has a history going back, at least, to the 1950's when Thomas Szasz, Barbara Wootton and others attacked the advance of psychiatry beyond the treatment of well defined mental disorders into areas of dysfunctional behaviour related to crime and delinquency.⁵ For Szasz and Wootton, 'science' was replacing traditional areas of social morality as the means distinguishing between the "undeniably mad" from those "who are simply unable to manage their lives". The distinction between 'mentally incompetent' and 'sinful' needs to be determined by social values. Allowing 'medical science' to encroach on this decision focuses attention on the individual instead of the environment as the source of the problem. As Wootton observes: "Always it is easier to put up a clinic than to pull down a slum." While insightful, the early contributions by Szasz and Wootton only examined the narrow confines of psychiatry where the social implications of medicalization are readily discernible. During the 1970's, the extension of these initial notions to a wider field of applications was initiated by Eliot Freidson and Irving Zola where the connection between medicalization and social control was established.⁶

See Table 1: Top 20 Pharma Products in Advertising (2005)

⁴ Some sources also include the medical insurance industry that processes payments for the bulk of medical services. This approach is not adopted in what follows, if only because the monopoly medical insurer in Canada are the federal and provincial governments.

⁵ Barbara Wootton, assisted by Vera G. Seal and Rosaling Chambers (1958), *Social Science and Social Pathology*, New York : Macmillan, 1959;. Thomas Szasz (1958), "Psychiatry, Ethics, and the Criminal Law. *Columbia Law Review*, 58 (February), 183-198; Thomas Szasz (1958). "Scientific Method and Social Role in Medicine and Psychiatry". *A.M.A. Archives of Internal Medicine*, 101(February), 228-238; Thomas Szasz (1961), *The Myth of Mental Illness*.

⁶ E. Freidson (1970), *Profession of Medicine*, New York: Dodd, Mead; I. Zola (1972), "Medicine as a institution of social control", *Sociology Review* 20: 487-504.

The identification of medicine as an institution of social control can be traced to Talcott Parsons.⁷ As such, development of the connection between social control and medicalization was consistent with traditional sociology where social control is a central concept. The observation that medicine had “nudged aside” or “replaced” religion as the dominant moral force in the social control of modern societies was a central theme in medicalization research surveyed in the influential 1992 review by Peter Conrad (“Medicalization and Social Control”). The lack of cohesion in this research is reflected in the considerable effort Conrad dedicates to the search for a precise definition of ‘medicalization’.⁸ Driven by the remarkable evolution of the medical profession in the last two decades, it is becoming gradually apparent that the medicalization concept is too diverse to be analysed with a unifying methodology.⁹ In particular, analytical advantage is gained if medicalization is dichotomized into two categories: social medicalization, dealing with the type of social control issues that originate with Szasz and Wootton; and, economic medicalization, dealing with the creation of markets for medical technology and professional services.

Since Zola, medicalization has been defined as a process where more and more aspects of everyday life come under medical dominion, influence and supervision. This broad definition of medicalization involves “the turning of non-medical problems into medical ones”.¹⁰ This process can occur for various reasons. Drawing a distinction between economic and social medicalization focuses attention on the ethical motives of the medical professionals involved in the process. Economic medicalization encompasses cases where the profit motive plays a substantive role in the transformation of non-medical problems into medical ones. Following Conrad and Leiter, this includes the direct-to-consumer marketing campaigns by pharmaceutical companies and the development of private medical markets. In contrast, social medicalization includes studies where the profit motive plays a lesser role, such as studies of spouse battering or

⁷ See T. Parsons (1951), *The Social System*. New York: Free Press.

⁸ Writing over a decade later, this lack of cohesion in the state of medicalization research is reflected by Sismondi (op.cit., p.153): “For the most part, medicalization is discussed in terms of the politics of professions, with medical professions gaining importance as they take control over the problems, and sometimes the lives and movements, of a typically disempowered group. Somewhat less frequently, medicalization is discussed in terms of the economics of healthcare industries, including associations of doctors, insurance companies, and drug companies; a few cases include analyses of depression...,hyperactivity...,osteoporosis...,ands exology. The means by which economic interests shape medical knowledge and medical discourse have not been well explored.”

⁹ P. Conrad, Peter and V. Leiter (2004), “Medicalization, Markets and Consumers”, *Journal of Health and Social Behavior* 45 (Supplement): 158-76.

¹⁰ 10 Sismondi (op. cit., p.153).

gender deviance. The classification of other areas of medicalization research depend on the methodological approach taken, such as studies of childbirth, infertility and abortion, where the profit motive may or may not be of central concern.

2. Medical Research and Corporate Marketing Strategies.

The moral and ethical implications of economic medicalization resound today in the television marketing campaigns by the pharmaceutical companies designed to put in place a public perception of illness and health consistent with the portfolio of prescription drug products on offer (see Table 1). Where bodies were once understood as normatively healthy and only sometimes ill, effective marketing has individuals seeing their bodies as inherently ill, and only able to be brought towards health with the effective medical treatment. The history of Viagra and the erectile dysfunction drugs attests to the ability of the direct-to-consumer marketing by pharmaceutical companies to transform a non-medical problem into a medical one. The treatment of risk factors for illness and not just the associated illness has also allowed pharmaceutical companies to dramatically increase the sales of prescription drugs. Given the difficulty of determining whether a good outcome has resulted from the perceived ‘risk’ being successfully treated, this is a potentially much more profitable area for pharmaceutical company marketing campaigns to pursue than the development of drugs that treat actual diseases (See Diagram 1 Canadian Drug Licencing).

Social medicalization research is concerned with encroachment of the medical profession into areas traditionally controlled by other professions, such as the legal profession for deviant behaviour or the ecclesiastic profession for reproductive decisions. This often leads to a sociological examination of issues surrounding the competition of the professions for social control. While the profit motive may play some role, the complexity of issues surrounding the ethics of the market place are not a central concern. Since the public policy disaster created by thalidomide in the 1960's, it has been recognized that medical research and development (R&D) is an area where the conflict of interests between private sector firms and those of government requires regulatory oversight. In the US, the Food and Drug Administration is the primary regulatory authority while, in Canada, this authority resides with Health Canada which is responsible of enforcement of the Food and Drug Act (the Act). The regulatory authority for

ethical issues under the Act resides with the “Review Ethics Board” (REB) which has a similar counterpart in the US with the “Institutional Review Board”.¹¹ In Canada, the REB’s represent the major health catchment regions across the country. Under the Act, REB approval is required to carry out clinical trials involving humans (see Diagram 1). The corporations seeking REB approval are, in most cases, multinationals that are involved in acquiring government approval to market patent protected drugs in a number of legal jurisdictions.

The *raison d’être* of the REB is to ensure that ethical norms of the general population are not put at risk by the private sector firms conducting the bulk of medical R&D that are motivated by the ethical standards of the marketplace. In this vein, implications of the profit motive include: the need to recoup research and development (R&D) expenditures as soon as possible; the need to recoup acquisition costs related to the takeover of other firms that have developed potentially marketable technologies for drugs or devices;¹² a desire to exploit first mover advantages where the danger of a ‘race to market’ with potentially competing innovative drugs or devices maybe apparent; the drive to develop alternative (off-label) applications and delivery mechanisms for existing drugs; and, attempts to extend drug or device patent protection by reformulations combining these drugs with other existing medications, e.g., combining a non-steroidal anti-inflammatory with an existing acid inhibiting drug to reduce gastric side effects. Faced with a limited time to patent expiration, there is great economic pressure on pharmaceutical companies to move drugs to market as quickly as possible. Rewards are more closely tied to the number of prescriptions written for a drug than to the incremental medical value of the treatment.

Once the regulatory infrastructure for conducting research through clinical trials is juxtaposed against the corporate requirement of profitability through successful marketing of pharmaceuticals or devices, the stage is set for serious ethical conflict to emerge between the

¹¹ In the Canadian Food and Drug Act, a “research ethics board” (REB) is defined as a body that is not affiliated with the sponsor, the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being. A REB has at least five members that includes: at least two members whose primary experience and expertise are in a scientific discipline, who have broad experience in the methods and areas of research to be approved and one of whom is from a medical discipline; one member knowledgeable in ethics; one member knowledgeable in Canadian laws relevant to the biomedical research to be approved; one member whose primary experience and expertise are in a non-scientific discipline; and one member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the sponsor or the site where the clinical trial is to be conducted.

¹² The best indicator of this appears to be the completion of Preclinical and Phase I and II trials since they seem to account for the substantial share of research failures.

players. This conflict is central to analysis of economic medicalization where the ethical norms of ‘science’ are confronted with the ethics of the market place. In science, accuracy of measurement and validity through replication are fundamental elements. In contrast, the objective of profitability is supported by research, biased or unbiased, that recommends prescription of the treatment on offer. Examples of such bias are accumulating. One estimate from the publicly funded Therapeutics Initiative, which reviews 25-33% of drugs for effectiveness on behalf of the Canadian federal government has suggested that economic interests may have produced significant bias in up to 90% of published drug literature. Another example is provided by Heres et al. where 33 company sponsored studies of second generation anti-psychotic drugs are examined. In ‘head to head’ studies involving competing products, the reported total outcome was in favour of the sponsor’s drug 90% of the time.¹³ Such an ‘empirical’ result is outside the bounds of scientific credibility.

The medical research literature abounds with examples of bias in empirical studies of pharmaceutical effectiveness such as: studies with fundamental design flaws where no control groups or placebo arms are involved; studies where poor comparators are used, e.g., the sponsored drug is compared to a placebo (no treatment) instead of the most effective comparator drug available;¹⁴ and studies where the sponsored drug is compared to an ineffective comparator that is given to the control arm instead of the most efficacious competitive drug on the market. Additional bias can be introduced by the method of comparison used. For example, economic cost comparisons are sometimes avoided when the effectiveness of new experimental drugs is being assessed. Due to large accumulated R&D expenses, such long patent-life drugs can be substantially more expensive than comparable predecessor drugs. Effectiveness measurement could emphasize, say, patient mortality instead of the increase in mortality compared to cheaper generic drugs that have comparable effectiveness. Sample bias can also be compromised through

¹³ S. Heres, S., J. Davis, K. Maino, E. Jetzinger, W. Kissling, and S. Leucht (2004), “Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics”, *American Journal of Psychiatry* 194: 185-194; M. Bhandari, M., J. Busse, D. Jackowski, V.. Montori, H. Schünemann, S. Sprague, D. Mears, E. Schemitsch, D. Heels-Ansdell and P.J. Devereaux (2004), “Association Between Industry Funding and Statistically Significant Pro-industry Findings in Medical and Surgical Randomized Trials”, *Canadian Medical Association Journal* 170: 477-480.

¹⁴ 14 Bero, L. and D. Rennie (1996), “Influences on the Quality of Published Drug Studies”, *International Journal of Technology Assessment in Health Care* 12: 209-237.

the impact of study entry criteria, such as excluding pregnant women or restricting ethnic minorities into the sample population.

Economic medicalization of research studies is a process where the traditional values associated with the scientific method are replaced by research ethics that reflect the values of the market place. While traditional scientific values demand the researcher be as objective as possible in order to reduce the possibility of bias in the interpretation of the observed data, the ethics of the marketplace are more concerned with abnormal financial gains (losses) associated with ‘positive’ (negative) research results. In statistical terms, economic medicalization occurs when there is a decided ethical bias towards unjust acceptance and against unjust rejection. One documented instance where this occurs is ‘publication bias’: a tendency to publish only favourable clinical trial results of an experimental drug. Corporate sponsors have little interest in providing negative information regarding a product in which they may have already invested millions of dollars. Even journal editors may show a predilection for publishing successful, as opposed to failed, clinical trial results.¹⁵ Consequently, the medical community observes the positive research study results for the drug that accumulate in the published literature rather than the failed trials of the drug which languish in the ‘file drawer’.

Another instance of economic medicalization is ‘muzzle clauses’ in the contracts of investigators involved in clinical trials. These clauses are intended to prevent researchers from releasing any information about the clinical trial without the sponsor’s permission. This can be problematic if the physician discovers significant safety concerns related to the trial. If the researcher releases the negative information, the terms of the muzzle clause are breached and a variety of undesirable outcomes can result. Examples of possible outcomes include: threats of civil lawsuits; the sponsoring company withdraws financial support for the researcher and, possibly, reduces or eliminates philanthropic contributions to the host institution; and, the sponsoring company engages outside experts to refute the researcher’s findings. However, if the researcher sits on the information the doctor-patient accord to act in the best interests of the research subjects recruited for the drug trial is breached. Many facets of muzzle clauses emerged in the the Nancy Olivieri versus Apotex case that received international coverage in medical and

¹⁵ A. Schafer (2004), “Biomedical Conflicts of Interest: A Defence of the Sequestration Thesis: Learning From the Cases of Nancy Olivieri and David Healy”, *Journal of Medical Ethics* 30: 8-24.

ethics journals and is used as a classic example of the failure to deal effectively with the problems posed by restricting negative results from drug trials.¹⁶

The controversy involving Apotex Inc., Dr. Nancy Olivieri and the Hospital for Sick Children in Toronto (the Hospital) originated in clinical studies of the drug L1 (deferiprone) that generated disputes between Apotex and Dr. Olivieri, between Dr. Olivieri and other investigators and between Dr. Olivieri and the Hospital. L1 was first synthesized in 1987 and a research study by Dr. Olivieri and Dr. Gideon Koren of L1 in patients at the Hospital began in 1989, funded by the federal government's Medical Research Council of Canada (MRC). When this funding ended in 1992, an alternative source of funding was received from Apotex. While the company was initially reluctant to get involved with the development of L1 because of its impaired patent status and because it produced serious side-effects in some patients, Apotex ultimately obtained a licence to develop L1 from the patent holder and a drug trial conducted by Olivieri and Koren was sponsored which involved patients with thalassemia major, a disorder that impacts hemoglobin production. Participants in the study were randomly assigned to receive either L1 or deferoxamine, the established treatment for iron toxicity. The randomized trial was constructed to compare the effects of the two drugs on body iron levels. The contract between the researchers and Apotex governing the drug trial contained a muzzle clause.

The details of the subsequent L1 drug trial are well known. There was tension between Dr. Olivieri and officials of Apotex almost from the beginning, at least partly due to differences in expectations between the investigators who viewed the trials as continuing research work done under the MRC grant and Apotex whose expectations were consistent with the usual procedures for the initiation and conduct of industry funded drug studies. While in April 1995, the investigators published a paper indicating a 'favorable effect of deferiprone on iron balance', by the autumn of 1995, some negative data were emerging from the compassionate use trial. This data was seen by Dr. Olivieri as a 'loss of response' or 'loss of efficacy' in some patients receiving L1. Apotex objected to this characterization, interpreting the findings as being due to variability in response that is seen with most drugs. In March 1996, Dr. Olivieri reported her findings of loss of response to the REB and was instructed to modify the patient information and consent forms and to advise physicians treating patients with L1 at other centers, of her findings.

¹⁶ 16 Schafer (op. cit.)

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In early May 1996, Apotex indicated to the REB that investigators in other centres involved in the drug trial did not agree with Dr. Olivieri's interpretation and that Apotex had convened an expert panel of international stature to review the data. On May 24, 1996, Apotex wrote to Olivieri and Koren informing them that Apotex was not renewing the trials contract which had expired some weeks earlier. In this communication, Apotex reminded the researchers of the contract's confidentiality provision that: "all information whether written or not, obtained or generated by the Investigators during the term of the LA-O1 [randomized trial] Agreement and for a period of one year thereafter, shall be and remain secret and confidential and shall not be disclosed in any manner to any third party except with the prior written consent of Apotex. Please be aware that Apotex will take all possible steps to ensure that these obligations of confidentiality are met and will vigorously pursue all legal remedies in the event there is any breach of these obligations." On the same date, Dr. Olivieri was informed that an additional consulting contract with Apotex would not be renewed and the same warning was issued to her about breaches of its confidentiality provisions.

Needless to say, Olivieri was not deterred by the muzzle clause. In July 1996, the expert panel appointed by Apotex produced a report that supported the Apotex interpretation of the variability in response to L1. Dr. Olivieri produced a commentary rebutting these findings and reaffirming the negative conclusions about the efficacy of L1. Starting in early December 1996, Dr. Olivieri began to disseminate the negative L1 results at a variety of professional conferences including the American Society of Hematology. In the time leading up to these presentations, Apotex indicated repeatedly that they did not concur in the findings that L1 caused liver fibrosis in some patients and would not consent to the submission of the abstracts for publication. Dr. Olivieri was again notified that she would be breaching the contract if she proceeded to do so. Apotex also questioned the data supporting the conclusion, and arranged to have an independent analysis done by a leading expert on liver pathology, Dr. Francesco Callea. This expert came to a different conclusion than Dr. Olivieri, finding that L1 did not exacerbate liver fibrosis. Much of the subsequent notoriety and public attention the case received was due to the desire of Olivieri to publicize the events.

Muzzle clauses are a relatively obvious implication of economic medicalization. Other implications are less obvious. Consider the issue of drug trial sample design. While concerns of public safety argue for a time series analysis of experimental medical products, economic

pressures to bring a drug to market as soon as possible result in a cross-sectional or static (as opposed to dynamic) analyses. This fosters large Phase 3 trials where sample sizes are substantial, but the elapsed time may be insufficient for dynamic or cumulative effects of the experimental product to emerge. Phase 4 or post-marketing trials however are longer term and much more effective at detecting these time series based cumulative effects. The problem is, there is no requirement that all Phase 4 post-marketing or tracking studies be conducted or reported. The tragic consequences of OxyContin, Neurontin, Paxil, Accutane, Baycol, Aprotinin and Vioxx speak clearly to the dangers of long-term cumulative effects that have emerged only after extended periods of time in the market place.¹⁷

Because drug and device firms are not obliged under the Act to carry out publicly vetted or publicly published phase 4 research programs the law and the ethical issues surrounding Phase 4 research clinical trials are ill defined. A company that is concerned about the longer term side effects of a drug might carry out a longitudinal tracking study as a means of exhibiting due diligence. If negative results were found, the company would arguably have an ethical responsibility to make those side effects known and, if serious enough, voluntarily pull the drug from the market. However, there is evidence that in some serious cases voluntary withdrawal did not happen, a consequence of the desire to avoid the multi-million dollar investment losses for the pharmaceutical company stockholders that can occur when such negative news is released to the capital market.¹⁸ In economic terms, a decision not to withdraw a drug (e.g., Vioxx) has to be weighed off against the danger of civil litigation associated with the damage done by the drug side effects. This legal-is-ethical condrum may also lead to effective Phase 4 trials not being carried out since, as in the case of Bayer, if no negative side effects are found then there is no obligation to report them publicly.¹⁹ Finally, with the rapid development of large scale data-bases in the last decade, Phase 4 studies can also be conducted in house using multivariate observational analysis, more-or-less ensuring the privacy of the Phase 4 statistical results and avoiding problems of public scrutiny.

Recent evidence suggests that some form of economic medicalization is happening in Phase 4 studies. In 2000, Phase 4 studies accounted for 3.1% of all clinical trials worldwide that

¹⁷ 17 A. Caplovitz (2006), "Turning Medicine into Snake Oil: How pharmaceutical marketers put patients at risk". New Jersey Public Interest Research Group Law and Policy Center: 1-52; Avorn, J. (2006). "'Dangerous Deception' Hiding the Evidence of Adverse Drug Effects". New England Journal of Medicine 355 (Nov.): 2169-2171.

¹⁸ 18 Caplovitz (ibid.); Avorn (ibid.)

¹⁹ 19 Avorn (ibid.)

were registered with the U.S. National Institutes of Health (USNIH 2008). In 2008, Phase 4 trials accounted for 16.7% of all registered trials. It is difficult to tell whether this increase was due to the increased registration Phase 4 trials or to an actual increase in the number of such studies. In this vein, evidence points to the increasing use of primary physicians to conduct Phase 4 trials where remuneration is paid for participation. At this point, it is unclear whether these studies constitute 'real research' with properly structured Phase 4 research protocols that would meet REB standards or whether they constitute 'drug seeding' marketing strategies. Two articles from Canadian Pharmaceutical Marketing certainly point to the latter hypothesis.²⁰ Both articles provide advice to pharmaceutical companies on how Phase 4 studies can be used to attract physician participation in order to generate new drug sales. This approach appears to be supported by the Andersen et al. where it is reported that general practitioners (GP's) were paid \$800 US per patient to recruit subjects for an asthma study. Study results indicated an increase in prescribing patterns of the trial sponsor's drug among the participating physicians. U.S National Institutes of Health data show Phase 4 trials in Canada increased from 3 in the year 2000 to 237 in 2008, a 7900% increase.²¹ As these are registered trials, REB research protocols would be satisfied and it is expected that the Phase 4 studies would make a legitimate contribution to the medical literature. However, this does not preclude a concomitant drug seeding motive in the studies.

4. Marketing to Physicians

Economic medicalization involves a complicated web of interaction between physicians, responsible for prescribing drugs and delivering medical care, and the pharmaceutical and medical device companies that supply the products that are essential to the practice of modern medicine. Understanding the marketing methods companies use to influence treatment selection assists in identifying sources of ethical conflict in the medical R&D process. One key marketing strategy revolves around influencing the opinion leaders. Applying this strategy to the case of medical drugs and devices, opinion leaders can be identified with groups such as specialists, research faculty, heavy prescribers in a drug/device category and product champions.

²⁰ 20 R. Deshpande, R. and S. El-Chibini (2005), "Scientific Marketing Offers a New Way to Get Prescribers", Canadian Pharmaceutical Marketing (Feb.): 37-38; R. Deshpande and S. El-Chibini (2004), "If You Build it will they come? Phase IV recruitment", Canadian Pharmaceutical Marketing, (Oct.): .31-32.

²¹ 21 United States National Institutes of Health, available from ClinicalTrials.gov website <<http://clinicaltrials.gov/ct2/search/map>>, Jan. 28, 2008.

Considerable effort is given to finding opinion leaders willing to speak favourably about a company's product. In many cases, opinion leaders derive financial gain from interacting with medical product marketers at a number of levels. Marketers try to influence opinion leaders because these groups, in turn, affect the purchasing habits of other buyers who respect the opinion leaders' knowledge base and authority in a particular area.

The lack of ethical transparency in the motivations of opinion leaders in this process raises a number of ethical issues.(see Table 2 Annual Spending on Drug Promotion by Type (2005)).

The points of interaction between opinion leaders and companies are numerous. Opinion leaders are retained to provide presentations regarding research results at various venues; delivered lectures at conferences are financed in whole or in part by the corporations that retain the opinion leader; acting as paid consultants to those corporations and; offering symposia for continuing medical education in their fields of expertise. These interactions, which are arguably the business of the participants, cause ethical concern when it is difficult to determine the degree of independence that the opinion leaders are able to exercise given the financial and personal relationships that have developed between themselves and the corporations with whom they interact. Concerns arise that these 'relationship marketing' strategies may positively influence physician perceptions of the corporation and the products on offer, e.g., in qualitative evaluations of drug efficacy.²² The extent of this marketing strategy is somewhat staggering. Excluding free drug samples, Campbell estimates that 78% of U.S. physicians have been financially involved with industry: 35% reimbursements; 18% consultancy; 16%speaking engagements; 9% advisory boards and; 3% clinical trials recruitment.²³

It is tempting to conclude that opinion leaders are of sufficient ethical stature that actual and substantive knowledge of the subject will dictate an unbiased reading of the evidence. However, it is not always clear whether published research by a given opinion leader is free from the influence of economic medicalization. In particular, 'ghost-writing' is a marketing/research strategy where a drug company will carry out research and then forward the manuscript to an author in attempt to secure their endorsement. Obviously, only those research results favourable

²² 22 A. Gross, A., P. Banting, L. Meredith and D. Ford (1993), *Business Marketing*, Boston, MA: Houghton Mifflin Company.

²³ 23 E. Campbell, E. (2007), "Doctors and Drug Companies: Scrutinizing Influential Relationships", *New England Journal of Medicine* 357 (Nov.): 1796-1797.

to the product are forwarded to the prospective author. By attaching a respected author's name to the research results, the company hopes to achieve more rapid acceptance of their drug/device in the marketplace than if they attempted to advertise the product themselves.²⁴ This strategy is particularly attractive to academic research faculty where publications in prestigious journals have considerable value to career progress. In turn, ghost-written and other positive published research permits the sales representatives of a drug or medical device company to bring these trial results to the prescribing physician in an effort to influence prescription pattern choices.

While the enlistment of opinion leaders plays a fundamental role in corporate marketing strategies, it has traditionally been the prescribing physician that drug companies need to influence the most. Though this approach has changed dramatically with the rise of direct-to-consumer marketing (see Table 2), the bulk of advertising and promotion spending is still targeted directly at physicians. A key element in this strategy is the 'detail man'. It is estimated that there is approximately one pharmaceutical company sales representative for every 10 doctors in most developed countries. The history of the modern detail man can be traced back to the 1940-1960 era when the prescription drug industry was in a period of enormous expansion.²⁵ To address the dramatic changes in the medical profession brought on by the advent of a host of new and important prescription drugs, detail men during the period were transformed "from specialized salesmen into quasi-professionals". The pharmaceutical companies recognized the value to drug sales if detail men could be seen as assistants to doctors, conveying useful information about important drug developments rather than being mere salesman for products. Greene argues that this change of image "required a careful negotiation around doctors' spaces, both figuratively and literally."

The lack of ethical transparency in the activities of detail men is apparent. Though detail men can not be seen as telling doctors what to prescribe, their role is ultimately to influence prescription behaviours. To do this, detail men want to be seen by physicians as allied professionals, consciously modelled as having the same ethical objectives as doctors. For example, Green reports that manuals for detail men reproduce parts of the American Medical Association's code of ethics. To be effective, detail men need to have the ability to interact with

²⁴ 24 D. Healy, D. (2004). "Shaping the Intimate: Influences on the Experience of Everyday Nerves", *Social Studies of Science* 34: 219-245.

²⁵ 25 J. Greene, J. (2004). "Attention to 'Details': Etiquette and the Pharmaceutical Salesmen in Postwar USA", *Social Studies of Science* 34: 271-92.

doctors, and require training to develop this ability. Detailing has to at least appear to educate, rather than merely to sell. In this process, the research pipeline of positive results are an invaluable tool for the detail men. Marketing to doctors often takes the form of getting doctors up to speed on the latest research. The range of techniques that can accomplish this goal includes not only marketing by pharmaceutical representatives, but also advertisements in professional journals, through continuing medical education conferences and so on.

Drug detailing and sampling are based more on pure marketing tactics. Yet, the suspicion of economic medicalization remains. Drug and medical device sales representatives bring research literature and clinical trial results to the doctors in efforts to influence their prescription pattern choices, while at the same time company funded research ensures that unsuccessful clinical trials not get published so physicians are exposed mainly to studies supportive of the drug or medical device.²⁶ Influential opinion leaders tend to be involved in the clinical trials that are positively predisposed toward the sponsoring company's drug or medical device.²⁷ This can have a positive affect on the perception of their peers toward the product.²⁸ Sales representatives attempt to influence physicians through 'relationship marketing' where personal interaction with physicians is used to influence decisions. Examples of relationship marketing include: drug or medical device representatives scrubbing in and attending surgeries; moving freely throughout emergency departments and wards and in some cases being involved in the delivery of drugs to patients;²⁹ and, company representatives paying 'preceptor fees' (in some cases C\$1000 per day) to accompany surgeons in operating rooms and clinics. The stated objective was to learn how physicians actually used the drug or medical device. The ethical concerns here are: the protection of patient confidentiality; and the issue of private funds flowing to doctors influencing physician choices of medical products.

A key element in marketing to physicians is the provision of free samples in order to impact on prescriptions patterns. Chew et al. concluded that the availability of drug samples led their primary physician respondents to prescribe drugs different from their preferred choice,

²⁶ 26 E. Turner, A. Matthews, E. Linardatos, R. Tell, and R. Rosenthal (2008). "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy", *New England Journal of Medicine* 358: 252-260.

²⁷ 27 M. Andersen, J. Kragstrup and J. Sondergaard (2006), "How Conducting a Clinical Trial Affects Physicians' Guideline Adherence and Drug Preferences", *Journal of the American Medical Association* 295 (June): 2759 -2764.

²⁸ 28 M. Steinman, L. Bero, M. Chren and S. Landefeld (2006). "Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents", *Annals of Internal Medicine* 145(August).

²⁹ 29 This raises the issue of the patient's right to confidentiality.

especially if it avoided costs to the patient.³⁰ Campbell et al. in a national U.S. survey reported that 78% of their 1,255 physician respondents had received free samples.³¹ Pharmaceutical companies do not undertake that level of free sample distribution unless it has a track record of producing results. Marketing research has long established that providing free samples is one of the strongest cues in terms of producing product trial and adoption. Medical products representatives donate substantial quantities of free samples to hospitals and clinics, presumably with the objective of slowly infiltrating the facility and subtly influencing staff usage patterns of drugs, devices and medical supplies. With the goal of promoting product efficacy, drug representatives aim to interact directly with hospital staff instead of, say, working through hospital pharmacologists who possess far greater knowledge of drug efficacy and safety and are much better equipped to evaluate drug alternatives.

One disturbing aspect of economic medicalization is the transformation of the process for doing clinical trials into exercises that are motivated more as marketing vehicles than needed R&D. One immediate advantage of this marketing strategy is that physicians can legitimately receive fees for the recruitment and tracking of subjects admitted into the clinical trials. In some instances these fees are not inconsequential. For example, Sismondi describes a US research study by Biovail that paid a fee of \$1000 for doctors, plus \$150 for office management expenses, for patient data when at least 11 of their patients renewed a prescription to Cardizem, a drug intended for long-term use.³² In this case, paying doctors to get patients started on a course of treatment could lead to substantial profits from these prescriptions. Doctors who signed up for the trial but who did not keep 11 patients on the drug received US\$250 for participation. According to ethicists who commented on the case, a US\$1000 payment to doctors was unusually high for a post-marketing research trial.

Another ethically disturbing aspect of economic medicalization is the evolution of off-label prescription drug usage. The prescription drug approval process is based on research and clinical trials where specific drugs and medical devices are approved by review boards for very specific applications. Once approved however, companies have economic incentives to promote use of the drug for other medical conditions without further research reviews by government.

³⁰ 30 L. Chew, T. O'Young, T Hazlet, K Bradley, C. Maynard, and D. Lessler (2000). "A Physician Survey of the Effect of Drug Sample Availability on Physicians' Behavior", *Journal of General Internal Medicine* 15: 478-483.

³¹ 31 Campbell et al. (op. cit.)

³² Sismondi (op cit., p.149)

Delays in seeking approval for alternative uses are consistent with obtaining a maximum revenue stream for a given product, if only because alternative uses can be a basis for a further round of patent protection. For example, Pfizer admitted guilt in the case of gabapentin (Neurontin), a drug originally intended for the treatment of epilepsy. The company subsequently used opinion leaders to market it to physicians for a range of other indications. Steinman et al. estimate the company spent \$40 million U.S. in advertising and promotion with 50-66% of that budget going to professional education between 1996 and 1998.³³ Steinman et al. (2006, p.286) shows a diagram demonstrating the increased market penetration achieved by selling gabapentin off-label. In general, Radley et al. estimate that 21% of all drug use in the U.S. among office based physicians was for off-label indications and that 73% of off-label uses lacked strong scientific evidence.³⁴

5. Ethical Transparency and REB Approval

Similar to other developed countries, in Canada the Act requires that drugs be subjected to clinical trials before being allowed for public sale. As part of this process it is required: that the research ethics board (REB) associated with each trial site approve the clinical trial protocol and the ‘informed consent letter’ that states the known risks and possible benefits arising to the health of clinical trial subjects as a result of their participation in the clinical trial. While there is no legislative statement of precisely how a research ethics board is to make decisions, it is conventional for decisions to be governed by the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans issued by the major government granting agencies, the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada. The Statement emphasizes the importance of acting first and foremost in the patient’s best interests. This is especially important because research subjects are often vulnerable people with serious or terminal diseases who are prepared to consent to almost any clinical trial out of desperation. REB’s are, in particular, sensitive to the protection of research subject’s rights that are delineated in the consent letters they are obliged to sign as a condition of participating in the medical trial.

³³ 33 Steinman et al. (op. cit.)

³⁴ 34 D. Radley, S. Finkelstein and R. Stafford (2006). “Off-Label Prescribing Among Office based Physicians”. Archives of Internal Medicine 166: 1021-1026.

These letters are in many cases drafted by the drug sponsor and presented by the doctors or their assistants to the patients for signature.

The significance of the REB in the clinical trial approval process was a central element in the Olivieri versus Apotex case. The REB responsible for the Hospital approved the initial round of research protocols for the trials. As per the Act, these protocols, prepared and signed by Apotex and the investigators, described the procedures for conducting the trials, information to be provided to patients about the risks and benefits of participating in the trials in obtaining informed consent, monitoring, safety measures, stopping rules and requirements for reporting unexpected findings and adverse reactions. Significantly, the protocols also contained provisions pertaining to confidentiality of information and publication rights that did not contain the muzzle clause which was contained in a separate 'trials contract' that Olivieri and Koren signed with Apotex. The REB approved the research protocols without knowledge of the separate contract. In March of 1996, when Olivieri discovered 'loss of response' in certain patients taking L1, this finding was reported to the REB. Olivieri was instructed by the REB to modify the patient information and consent forms and to advise physicians in the clinical trial treating patients with L1 of the findings. The lead doctor in the trial from Apotex asked Olivieri to convey the contrary Apotex view to the REB. Apotex also submitted information directly to the REB.

At this point in the Olivieri case, the ethical transparency becomes murky. Olivieri had only reported a 'loss of response' to the REB in March 1996. It was not until February 1997, after presenting the trial results at medical conferences, that Olivieri reported the more serious conclusion of liver toxicity to the REB. This is directly contrary to the requirement that adverse drug reactions be reported promptly. In defence, Olivieri indicated that the advice of legal council was to delay reporting to the REB. Confronted with the conflict between the two main partners in the clinical trial, in March 1996 the Chair of the REB informed Apotex that "the Research Ethics Board does not act as an intermediary between the investigator and the sponsoring company when different opinions arise. Consequently your correspondence should be directed to Dr. Olivieri for resolution."³⁵ The REB formulated this position in consultation with Olivieri. In early May 1996, Apotex notifies the REB that investigators in other centres did not agree with Olivieri's interpretation of the trial results. In July 1996, Apotex sent a copy of the expert panel's report to the REB which then supported the Apotex interpretation of the variability

³⁵ 35 This quote is taken from the Naimark Report.

in response to L1. Olivieri later sent a commentary to the REB rebutting the findings of the expert panel and reaffirming her conclusions about the efficacy of L1.

The footprints of REB decisions are everywhere in the notorious Olivieri versus Apotex. Throughout the case, the REB is kept in the loop and is required at various points to make an ethical determination of the changing situation. Under the Act, REB's can interdict the drug and medical device producers at any point between preclinical and Phase 3 trials. For clinical trials research conducted in Canada, without the REB approval and the successful completion of the trials the medical product will not receive clearance from the Federal Government for marketing in Canada. In making REB decisions, the evidence of potential ethical conflicts associated with the marketing of medical products and pharmaceuticals needs to be balanced against the profit-driven private sector sponsored research that has provided important amounts of needed capital for medical products and drug investigation as well as clinical trials that yielded significant sometimes dramatic contributions to patient health. The challenge for REB's is to create a sieve of sufficiently fine mesh such that research of questionable ethical standards is interdicted while allowing to pass, and indeed encourage, other research agendas that have the potential to make substantial contributions to medicine. The 'Naimark Report' on the Olivieri case prepared for the trustees of the Hospital for Sick Children concluded: "Consideration needs to be given to strengthening the Research Ethics Board and further developing its policies, procedures and mechanisms of evaluation so that it can meet the challenge of increasing demands. Special attention must be given to monitoring of compliance with REB decisions and with standards of good clinical practice, and the role of clinical supervisors in these matters."

Unfortunately, the Act provides no guidance on how the REB is to react to the various faces of economic medicalization. How to proceed in the face of potentially unethical research programs driven by corporate marketing strategies? Consider the post-approval Biovail Cardizem trial with the \$1000 payment to physicians for renewing prescriptions. This trial met the ethical requirements set out in US federal regulations for research trials. The stated purpose of the trial was to provide data that would help 'in designing future clinical trial programs'. The results of the study would eventually be published. However, it is now known that the program was originally presented as a marketing campaign, and was being handled by Biovail's sales department and sales force. How is the REB to determine how the physician balances research obligations with financial remuneration from the sponsor? REB's exercise authority primarily

where institutional facilities are involved, when clinical trials are conducted using patients at publicly funded hospitals, community clinics, and extended care facilities among others. The ethical line of REB intervention for clinical trials is currently determined by whether the physician is conducting a study independently out of a private office or whether the subjects have been recruited, or will be treated, in a publicly funded facility.

Given the current regulatory structure for drug approval in Canada, there are many areas where the negative public policy impact of economic medicalization cannot be effectively countered with REB oversight alone. For example, REB's have no control over the influential effects of communications that flow from the opinion leaders—specialists, academic researchers and product champions—to the larger body of practicing primary care physicians. A significant body of research in marketing at both the consumer and B2B levels is unambiguous regarding the influential impact that opinion leaders have on the purchasing habits of other buyers. REB's can do little more than be concerned about the ethical impact of relationship marketing strategies being used by corporations and the impact this can have on the opinion leaders who will in turn, influence other physicians. For example, it is difficult to assess the effect on qualitative research results when: specialists and researchers who carry out the phase 1 to 3 clinical trials receive remuneration for recruiting trial subjects; or when remuneration is paid to specialists and product champions to lecture at conferences, continuing medical education programs and symposia about a sponsor's drug; or when companies provide medical grants supporting researchers in other areas or make large contributions to academic institutions that employ the researchers. It is difficult to resolve the ethical issue of whether there is a less than fully arms length relationship between the participants.

Discernible trends in the pattern of economic medicalization indicate a number of flash points that threaten to undermine the validity of the present medical R&D clinical trial approval process. One such flash point is associated with phase 4 or post-approval research studies. Currently, there is no requirement that results of such studies need to be released or even that such trials be conducted according to REB approved protocols. In situations where negative or ineffective results are found, companies will be reluctant to release such results and, without REB oversight, will not be required to do so. Two particularly egregious cases where this has occurred are the Bayer admitting to a 'mistake' in suppressing a study that showed dangerous side-effects associated with the drug Baycol and Merck's suppression of studies that showed

Vioxx quadrupled the risk of myocardial infarction.³⁶ These studies only came to light because the adverse negative reaction spread over a large population was sufficiently detectable by other means. At present, the number of unregistered phase 4 trials in Canada is not known, nor is the amount of remuneration flowing to physicians who enroll patients in these ‘trials’.

Unfortunately, aiming to increase the reach and depth of ethical oversight in order to prevent questionable research practices may, in the end, be self-defeating. Faced with rising costs associated with obtaining clinical trial approval in developing countries, pharmaceutical companies are moving certain types of medical R&D offshore to third world jurisdictions where the ethical requirements of the drug approval process are substantially less due to lower costs, lax regulations and uneducated research subjects that make for more freedom in research design and lower all-in costs of doing experimental trials.³⁷ Arguably questionable randomization procedures have been observed in some research protocols used in third world countries. The classic case involved the randomization of African subjects to a placebo arm of the study for an HIV drug when there was an existing ‘gold standard’ treatment available for comparison. Consequently certain HIV pregnant women received no treatment at all under the placebo arm of the study when a live-saving drug could have been administered without adversely affecting the trial results. Cost effectiveness in medical R&D seems an appropriate iteration on the economic medicalization theme.

A final point of ethical concern can be found in the now rapidly emerging development of private research data bases. Such data bases are being created when clinical trials request that subjects give blood and tissue samples for ‘future research’. Modern technology permits these samples to be analysed to the molecular and genetic level and this information entered into the data base. Such requests for blood and tissue samples are now commonplace in the consent forms and clinical trial protocols submitted to REB’s. The data bases are conducive to in-house analysis by pharmaceutical companies. At present, even though the data were obtained from an approved clinical trial, there is no process to ensure that negative findings associated with experimental drugs obtained through exploitation of the data base will be subjected to public

³⁶ 36 Avorn (op. cit.)

³⁷ 37 P. O’Neil (2008). “Ethics Guidelines for Clinical Trials to be Revised”, Canadian Medical Association Journal (Jan.)

scrutiny by the REB.³⁸ It is fascinating that, as with other areas of marketing research, large data bases appear to have become the currency of R&D in the new millennium.

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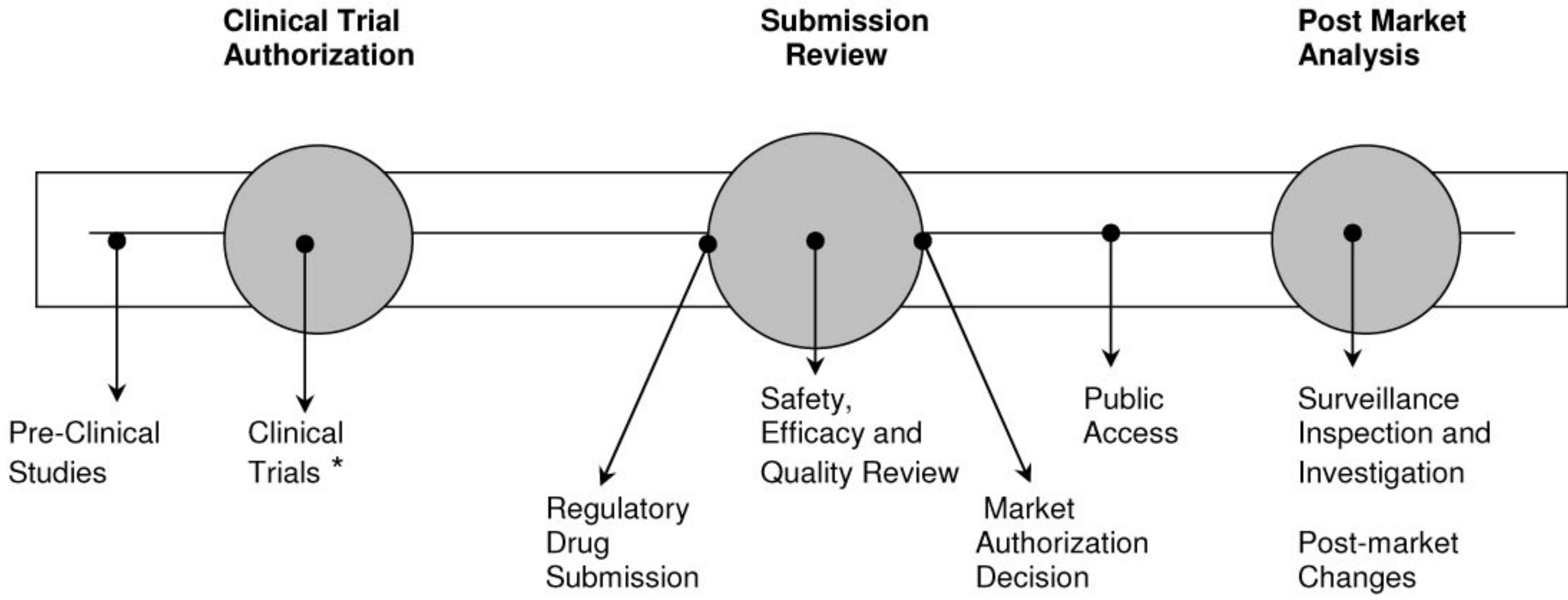
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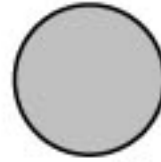
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Diagram 1
Canadian Drug and Device Licensing Process



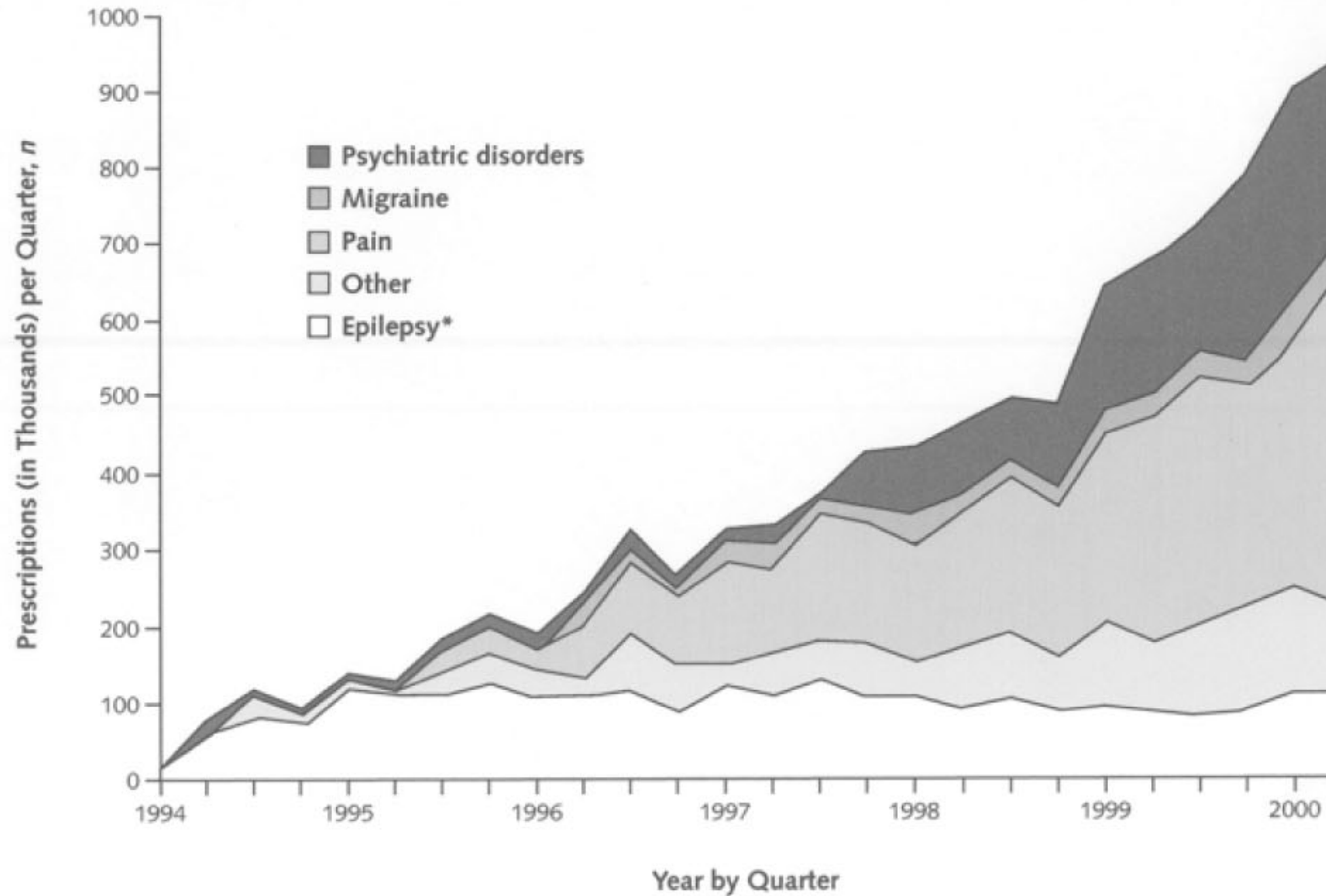
 = Health Canada's current regulatory authority

* Review Ethics Board approval is required to initiate this step.

Adapted Jan. 29, 2008 from Health Canada website:
< http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/index_e.html >

Diagram 2

Figure 1. Prescriptions for gabapentin, by diagnostic category.



Estimates of diagnosis-linked prescribing provided by Pfizer, Inc. (2–4). Each diagnosis was assigned to a diagnostic category by the authors. *Adjunctive treatment of epilepsy in adults older than age 12 years was the only U.S. Food and Drug Administration–approved use of gabapentin during the time period shown.

Source: P. 286 Steinman et al., “Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents” *Annals of Internal Medicine* Volume 145 Number 4, August 2006.

Table 1
Top 20 Pharmaceutical Products in Terms of Spending on Direct-to-Consumer Advertising in 2005.*

<u>Drug</u>	<u>Company</u>	<u>Therapeutic Category</u>	<u>Spending</u> <i>millions \$</i>	<u>FDA</u> <u>Approval</u>	<u>Year That</u> <u>Campaign Started</u>
Nexium (esomeprazole)	AstraZeneca	Proton-pump inhibitor	224	Feb. 2000	2001
Lunesta (eszopiclone)	Sepracor	Hypnotic-sedative	214	Dec. 2004	2005
Vytorin (ezetimibe-simvastatin)	Merck/Schering-Plough	Cholesterol absorption blocker-HMG-CoA reductase inhibitor	155	July 2004	2004
Crestor (rosuvastatin)	AstraZeneca	HMG-CoA reductase inhibitor	144	Aug. 2003	2004
Advair (fluticasone and salmeterol)	GlaxoSmithKline	Corticosteroid- β -adrenergic-receptor agonist	137	Aug. 2000	2001
Nasonex (mometasone)	Schering-Plough	Corticosteroid	124	Dec. 1997	1998
Flonase (fluticasone)	GlaxoSmithKline	Corticosteroid	111	Oct. 1994	1995
Lamisil (terbinafine)	Novartis	Allylamine antifungal	110	May 1996	1997
Plavix (clopidogrel)	Bristol-Myers Squibb/Sanofi	Platelet-aggregation antagonist	110	Nov. 1997	2001
Cialis (tadalafil)	Lilly	ICOS PDE5 inhibitor	110	Nov. 2003	2004
Wellbutrin XL (bupropion)	GlaxoSmithKline	Dopamine reuptake inhibitor-SNRI	108	Aug. 2003	2004
Singulair (montelukast)	Merck	Leukotriene D4-receptor antagonist	105	Feb. 1998	1998
Lipitor (atorvastatin)	Pfizer	HMG-CoA reductase inhibitor	93	Dec. 1996	1998
Ambien (zolpidem)	Sanofi-Aventis	Hypnotic-sedative	88	Sept. 2005	2005
Humira (adalimumab)	Abbott	Monoclonal antibody	88	Dec. 2002	2003
Imitrex (sumatriptan)	GlaxoSmithKline	Vascular 5-HT ₁ -receptor agonist	82	Aug. 1997	1998
Viagra (sildenafil)	Pfizer	PDE5 inhibitor	80	March 1998	1998
Neulasta (pegfilgrastim)	Amgen	G-CSF analogue	74	Jan. 2002	2002
Valtrex (valacyclovir)	GlaxoSmithKline	DNA polymerase inhibitor	72	June 1995	1996
Prevacid (lansoprazole)	TAP	Proton-pump inhibitor	71	May 1995	2000

* Adapted from Donohue et al. (op. cit., p.678).

Table 2
Annual Spending on Advertising and Promotion to Health Professionals, 1996–2005.*

Variable	Annual Spending									
	<u>1996</u>	<u>1997</u>	<u>1998</u>	<u>1999</u>	<u>2000</u>	<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>2004</u>	<u>2005</u>
<i>Direct-to-consumer advertising</i>										
Total spending (millions of \$)	985	1,301	1,578	2,166	2,798	2,954	2,864	3,478	4,160	4,237
Percentage of sales	1.2	1.5	1.6	1.8	2.1	2.0	1.9	2.2	2.5	2.6
<i>Professional promotion</i>										
Total spending (millions of \$)										
Detailing	3,747	4,093	4,861	5,064	5,447	6,055	6,731	7,364	7,585	6,777
Journal advertising	571	621	597	551	549	469	474	476	516	429
Percentage of sales	5.4	5.4	5.6	4.7	4.6	4.5	4.8	5.0	4.9	4.4
<i>Free samples</i>										
Total retail value (millions of \$)	6,104	7,358	7,910	8,476	9,021	11,539	12,928	14,362	16,404	18,438
Percentage of sales	7.6	8.4	8.1	7.1	6.9	8.0	8.6	9.1	9.9	11.2
<i>Total promotion</i>										
Total spending (millions of \$)	11,407	13,373	14,946	16,257	17,815	21,018	22,997	25,680	28,664	29,881
Percentage of sales	14.2	15.3	15.3	13.7	13.6	14.6	15.2	16.3	17.2	18.2

* Data on promotional spending are from IMS Health (www.imshealth.com); data on sales are from PhRMA's annual report. All data adjusted to 2005 dollars by Consumer Price Index deflation. Spending on free samples for 2005 was estimated by Donohue et al. (op. cit., p.676) on the basis of growth and spending rates from the previous 3 years.