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Ethical Transparency and Economic Medicalization

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ABSTRACT. This article introduces the concept of economic medicalization where non-medical problems are transformed into medical problems in order to achieve the objective of corporate shareholder wealth maximization. Following an overview of the differences in ethical norms applicable to medical ethics and business ethics, the economic medicalization of medical research practice and publication is examined in some detail. This motivates a general discussion of the problems involved in the ethical approval process for medical research that balances the interests of both business and government in the market for medical products and services.

KEY WORDS: shareholder wealth maximization, medicalization, bioethics, medical ethics

Medical research and development (R&D) is an area where the interests of private sector firms often conflict with those of governments (Angell, 2004; Moynihan and Cassels, 2005; Robbins-Roth, 2000). More precisely, the private sector firms conducting the bulk of medical R&D are motivated by the ethical standards of the marketplace (Poitras, 1994).[1] These standards differ from those of government which is an advocate for patients as well as having some control of the health care system through publicly funded medical care and drug plans. In this environment, there is a strong incentive for corporations to influence the public perception of the efficacy of certain drugs and medical devices (Avorn, 2006). There has been accumulating evidence that current levels of ethical disclosure do not make it possible to separate legitimate medical R&D from a corporate strategy of marketing patent protected medical products to physicians and, more recently, directly to consumers (Sismondo, 2004; Thompson et al., 2001; Turner et al., 2008). This article examines the economic medicalization of medical research practice and publication in order 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 market for medical products and services.

Medical ethics, bioethics and business ethics

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 profession.[2] Significantly, because the source of capital for the pharmaceutical industry is the global financial markets, the primary ethical motivations of this important player in the medical profession differs substantively 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 ethical motivations within the medical profession create a 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?

Due to the diverse and competing ethical norms that impact medical research, it is not easy to discern the de facto objectives driving the research. There is an ethical transparency problem. Doctors are bound by the ethics of professional fiduciary responsibility. In addition to specifying nine principles of medical ethics, the American Medical Association (AMA) provides detailed opinions on ethical behaviour for specific situations, e.g. conflicts of interest in biomedical research (AMA, 2006). These principles can be traced to the Hippocratic oath and the code of medical ethics introduced by Thomas Percival and John Gregory in the early eighteenth century. Though the code has evolved considerably from these early beginnings, basic principles still remain: physicians should base clinical practice and research on the best science available; individual self-interest is secondary to the well being of the patient; and, medical knowledge is a public trust to be used to the benefit of patients and society, e.g., Davidoff et al. (1995). These principles inform the institutional process for ethical approval of medical research as reflected, for the U.S., in Title 45 Code of Federal Regulations, Pt. 46 (45 CFR): obtain informed consent; protect the privacy of patient medical information; and, do no harm.

In contrast to the long established field of medical ethics, bioethics is a product of the relentless progress of modern biotechnology, e.g. Dhanda (2002), McGee (2003), Eaton (2004, 2008). Designed primarily for ensuring professional conduct by physicians, traditional medical ethics is not able to provide sufficient guidance to deal with the inter-disciplinary aspects of ethical problems raised by research into areas, such as: cloning; stem cells; genetic modification of foods; DNA data banking; genetic manipulation of human DNA; and, testing for genetic markers. Biotechnology has also impacted research areas that have long-standing social and religious significance, such as abortion, euthanasia and the determination of death. While medical ethics has considerable interest in such research areas and issues, bioethics goes beyond medical ethics to incorporate knowledge from moral philosophy, law, sociology, molecular biology, economics and other subjects. Central to the issues confronting bioethics is the justification for introducing new technologies. In practice, this ethical problem is confounded by the commercial aspects involved in developing these technologies. The substantial capital investments required for biotechnology advances dictate that bioethics also address the implications of corporate decision making.

In a sense, bioethics requires knowledge of business ethics. Some of the largest multinational corporations in the world are directly involved in the market for medical products and services. Conceptually, these corporations pursue strategies consistent with shareholder wealth maximization (SWM). However, there are layers of regulatory oversight that restrict unfettered activity. In the U.S., this oversight includes the ethical approval process for medical research embodied in 45 CFR that empowers the Institutional Review Board (IRB).[3] Following Poitras (1994), the goal of SWM depends on the future common stock price and, as such, does not have ethical transparency. Some assumption about the efficiency of the stock market in valuing ethical concerns is required. Ultimately, it is difficult to expect much more than an 'ethical-is-legal' approach to corporate decisions regarding medical research and development if SWM is the goal. Significantly higher ethical standards come at a financial cost that impacts corporate profitability undermining achievement of SWM. In setting the legal environment, governments are inclined to adhere to utilitarian ethics where decisions are made on the basis of cost-benefit calculations. The precise method of determining costs and benefits can depend on a range of political and social factors, not just a dollar and sense calculation. History suggests that crisis management, e.g. the thalidomide tragedy, is the primary motivation for substantive changes in the legal and regulatory framework.

The medicalization of society

The concept of medicalization has a history going back, at least, to the 1950s 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 (Szasz, 1958a, b, 1961; Wootton, 1959). 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 1970s, 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 (Freidson, 1970; Zola, 1972).

The identification of medicine as an institution of social control can be traced to Parsons (1951). 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 Conrad (1992). The lack of cohesion in this research is reflected in the considerable effort Conrad dedicates to the search for a precise definition of 'medicalization'. 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 analyzed with a unifying methodology (Conrad, 2007; Conrad and Leiter, 2004; Davis, 2006). 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''(Sismondi, 2004, p. 153). 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 (2004), this includes the direct-to-consumer marketing campaigns by pharmaceutical companies and the development of private medical markets. Healy (2004) examines the ''marketing of disease''. Conrad (2007) extends the list of categories consistent with economic medicalization, including: senior male disorders, such as andropause, baldness and erectile dysfunction; behavioral disorders, such as hyperactivity in children and adult ADHD; and, biomedical enhancements, such as human growth hormone and steroids. Jones and Hagtvelt (2008) detail the tragedy that economic medicalization has produced in the development of treatments for malaria. While a cost effective approach would be to eradicate the mosquito borne parasite by inoculating the local population, available treatments are centred on the more profitable Western visitors and ex-patriots sojourning in those regions where malaria is prevalent.

The implications of economic medicalization extend beyond the confines of medical ethics into the realms of bioethics and business ethics. This difference in ethical motivations of participants distinguishes economic medicalization from social medicalization. As such, when a significant participant is motivated by considerations of SWM, then economic medicalization could occur. Ethical conduct in medical research and development for a corporation pursuing SWM can conflict with the norms of medical ethics. Social medicalization is more concerned with the social ethics involved in different interpretations of what constitutes medical ethics, e.g. with regard to doing possible harm to medical subjects. Though both concepts of medicalization have elements that fall within the confines of bioethics, the high capital costs associated with biotechnology indicate that economic medicalization will typically be a more central concern. While the ethical approval process incorporated into government regulations is aimed at maintaining standards of medical ethics, lack of ethical transparency makes it difficult to discern motivations of medical professionals involved. Insofar as scientific norms of statistical evaluation and the like are being violated to sustain marketing objectives, then economic

medicalization is in conflict with medical ethics. The ethical issues confronting the corporation are less clear. Where is the line to be drawn between adhering to SWM and the violation of medical and social ethics?

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 I). 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' medical outcome has resulted from the perceived 'risk' being successfully treated, the creation and treatment of perceived health risks is potentially much more profitable area for pharmaceutical company marketing campaigns to pursue than the development of drugs that treat actual diseases. While this is an ethically acceptable outcome for the corporation pursuing SWM, it arguably conflicts with basic principles of medical ethics.

Since the public policy disaster created by thalidomide in the 1960s, it has been recognized that medical research and development (R&D) is an area where the conflict of interests between profit maximizing private sector firms and those of government requires strict regulatory oversight.[4] Within the U.S., the specific regulations involved vary depending on the particular type medical product or device. For example, regulatory oversight of the direct-to-consumer marketing of genetic testing kits in the U.S. would involve the Federal Trade Commission, the Centers for Disease Control, the Food and Drug Administration (FDA) and the state health agencies (Berg and Fryer-Edwards, 2008, p. 27). In the oversight process for public sale of prescription drugs and most medical devices, the FDA is the primary regulatory authority in the U.S. Similar bodies can be found in other jurisdictions. For example, in Canada primary regulatory authority resides with Health Canada which is responsible for enforcement of the Canada Food and Drug Act. In the oversight process, the regulatory authority for ethical issues resides with the IRB (U.S.) or similar body (''Review Ethics Board'' in Canada).

Consistent with the code of medical ethics, the *raison d'etre* of the IRB is to ensure that ethical norms regarding the treatment of human subjects 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. The role of the IRB in monitoring other types of ethically questionable research activities is less clear. In this vein, ethical difficulties arising from the corporate pursuit of the SWM could result from: the need to recoup 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;[5] a desire to exploit first mover advantages where the danger of a 'race to market' with potentially competing innovative drugs or devices may be 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. Pharmaceutical companies are faced with a limited time to patent expiration following the arduous and time consuming Phase 1–Phase 3 process of securing approval to sell a new drug to the public.[6] There is great economic pressure on pharmaceutical companies to move drugs to market as quickly as possible. Commercial 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

TABLE I

U.S. Sales Revenues and promotional spending for leading therapeutic classes of drugs, 2005[a]

Drug type	U.S. Sales Revenues	Total promotional spending (millions of dollars)	Percentage of sales	# Drugs using DTC	Type of promotion (%)		
					Direct-to-consumer advertising	Detailing	Professional meetings and events
HMG-CoA reductase inhibitors	16,000	859	5	4	34	52	11
Proton-pump inhibitors	12,900	884	7	4	34	57	7
SSRIs or SNRIs	12,500	1,018	8	6	12	68	15
Antipsychotic agents	10,500	513	5	4	10	64	21
Erythropoietin	8,700	100	1	2	31	45	12
Seizure-disorder agents	8,000	348	4	3	12	65	16
Angiotensin II antagonists	5,000	598	12	0	0	78	19
Calcium-channel blockers	4,600	94	2	0	0	79	18
ACE inhibitors	3,800	251	7	1	2	71	24
COX-2 inhibitors	1,800	299	17	1	4	78	16

[a]Adapted from Donohue et al. (2007, p. 677). Data on direct-to-consumer advertising are from TNS Media; data on detailing, professional meetings and events, journal advertising, and online promotions to physicians are from Verispan; and data on sales revenues are from IMS Health. Leading therapeutic classes of drugs were identified on the basis of publicly available IMS Health rankings of therapeutic classes according to spending for 2004.

successful marketing of pharmaceuticals or devices, the stage is set for serious ethical conflict to emerge between the players. This conflict is central to analysis of economic medicalization where the norms of 'science' embodied in medical ethics are confronted with the ethics of the market place and SWM. 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 (Bhandari et al., 2004; Heres et al., 2004). Such an 'empirical' result is outside the bounds of scientific credibility. The conflict between medical ethics and SWM is apparent.

Economic medicalization of research studies

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 (Bero and Rennie, 1996); 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 the impact of study entry criteria, such as excluding pregnant women or restricting the inclusion of 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 the traditional scientific values embodied in medical ethics 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 require firms to be fundamentally concerned with abnormal gains (losses) associated with 'positive' (negative) research results. In statistical terms, economic medicalization occurs because there is a decided 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 (Schafer, 2004). 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 ethically 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 Nancy Olivieri versus Apotex case that received international coverage in medical and 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 (Schafer, 2004; Thompson et al., 2001).

Muzzle clauses are a relatively obvious implication of economic medicalization. Other implications are less obvious. Consider the issue of clinical 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. Yet, current regulations impose few requirements that Phase 4 post-marketing or tracking studies be conducted or reported. The tragic consequences of OcyContin, Neurontin, Paxil, Accutane, Baycol (Caplovitz, 2006), Aprotinin and Vioxx (Avorn, 2006) speak clearly to the dangers of long-term cumulative effects that have emerged only after extended periods of time in the market place.

When drug and device firms are not obliged to carry out publicly vetted or published phase 4 research programs, the law and the ethical issues surrounding Phase 4 research clinical trials become 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 have an ethical-is-legal responsibility to make those side effects known and, if serious enough, voluntarily pull the drug from the market. However, even in cases

with such a limited ethical threshold, 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 (Avorn, 2006; Caplovitz, 2006). 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 ethical-is-legal conundrum 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 (Avorn, 2006). 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 to Phase 4 studies. In 2000, Phase 4 studies accounted for 3.1% of all clinical trials worldwide that were registered with the U.S. National Institutes of Health. In 2008, Phase 4 trials accounted for 16.7% of all registered trials (USNIH, 2008). It is difficult to tell whether this increase was due to the increased registration of 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 compensation is paid to the physician for enrolling patients in the study. At this point, it is unclear whether these studies constitute 'real research' with properly structured Phase 4 research protocols that would meet IRB standards or whether they constitute 'drug seeding' marketing strategies. Deshpande and El-Chibini (2005) provides advice to pharmaceutical companies on how Phase 4 studies can be used to attract physician participation in order to generate new drug sales. Use of a drug-seeding approach to Phase 4 trials appears in Andersen et al. (2006) where it is reported that when general practitioners (GPs) were paid $800 US per patient to recruit subjects for an asthma study, there was an increase in the prescribing patterns of the trial sponsor's drug among the participating doctors. This outcome could be due to physician learning about the efficacy of the drug or to financial self-interest. The lack of ethical transparency makes it difficult to determine motivations.

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. Considerable effort is given to find 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.

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 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 with specific corporations. 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

(Gross et al., 1993). The extent of this marketing strategy is somewhat staggering. Excluding free drug samples, Campbell (2007), in a national U.S. survey of 1,255 physicians, estimates: 78% have been financially involved with industry: 35% received reimbursements; 18% were paid consultancy fees; 16% were paid for speaking engagements; 9% paid for participating on advisory boards and; 3% were paid for clinical trials recruitment.

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 scientific 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 (Lynch, 2004). Obviously, only those research results favourable 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 (Healy, 2004). 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 is 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 II), 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. In order 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'' (Greene, 2004). 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 salesmen for products. Greene (2004) 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 cannot be seen as telling doctors what to prescribe, their role is ultimately to influence prescription behaviours. In order 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 AMA's code of ethics. To be effective, detail men need to have the ability to interact with doctors, and require training to develop this ability. Detailing has to at least appear to educate, rather than merely to sell. In this process, a research pipeline of positive results is 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, continuing provision of medical education conferences and so on.

The reliance of drug detailing and sampling on pure marketing tactics raises suspicion of unethical economic medicalization. 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 (Turner et al., 2008). Influential opinion leaders tend to be involved in the clinical trials that are positively predisposed toward the sponsoring company's drug or medical device (Andersen, 2006). This can have a positive affect on the perception of their peers toward the product (Steinman et al., 2006). Sales representatives attempt

TABLE II

Annual spending on advertising and promotion to health professionals, 1996–2005[a]

Variable	Annual spending									
	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Direct-to-consumer advertising										
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
Professional promotion										
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
Free samples										
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
Total promotion										
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

[a]Data on promotional spending are from IMS Health (http://www.imshealth.com); data on sales are from PhRMAs 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. (2007, p. 676) on the basis of growth and spending rates from the previous 3 years.

to influence physicians through 'relationship marketing' where personal interaction with physicians is used to influence decisions, (Meredith, 2000). 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; and, company representatives paying 'preceptor fees' (in some cases C$1000 per day) to accompany surgeons in operating rooms and clinics. The stated objective is to learn how physicians actually used the drug or medical device (Jones, 2007). Yet, the protection of patient confidentiality and the issue of private funds flowing to doctors influencing physician choices of medical products raises serious concerns for medical ethics.

A key element in marketing to physicians is the provision of free samples in order to impact on prescriptions patterns. Chew et al. (2000) concluded that the availability of drug samples led their primary physician respondents to prescribe drugs different from their preferred choice, especially if it avoided costs to the patient. Campbell et al. (2007) reports that 78% of their 1,255 physician respondents had received free samples. 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 (2004, p. 19) describes a U.S. 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. 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 medical ethicists who commented on the case, a US$1000 payment to doctors was unusually high for a post-marketing research trial.

Another disturbing aspect of economic medicalization for medical ethics 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. 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. (2006) 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. In general, Radley et al. (2006) 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.

Disturbing trends in economic medicalization

Unfortunately, the current regulatory structure for approval of drugs and medical devices is ill-suited 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 U.S. 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 IRB to determine how the physician balances research obligations with financial remuneration from the sponsor? IRBs 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 IRB intervention for, say, Phase 4 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.

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 IRB approved protocols. In situations where negative or ineffective results are found, companies will be reluctant to release such results and, without regulatory oversight, are not be required to do so. Two particularly egregious cases where this has occurred are 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 doubled the risk of myocardial infarction and stroke (Avorn, 2006). 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 both in the U.S. and globally is not known, nor is the amount of remuneration flowing to physicians who enroll patients in these 'trials'.

Ironically, 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 (O'Neil, 2008). 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 life-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 flashpoint can be found in the now rapidly emerging development of private research data bases. Such data bases are being created when clinical trials request subjects give blood and tissue samples for 'future research'. Modern technology permits these samples to be analyzed to the molecular and genetic level and this information entered into the database. Such requests for blood and tissue samples are now commonplace in the consent forms and clinical trial protocols submitted to IRBs. 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 database will be subjected to public scrutiny by the IRB (Avorn, 2006). Combined with direct-to-consumer marketing and the approval of genetic test kits for consumers, such data bases could provide a powerful tool for economic medicalization. Such developments would take place largely outside the current regulatory framework for the ethical approval of medical research.

Notes

[1] Subject to some qualifications, such as the assumption of no agency costs, the primary corporate objective is to maximize the expected utility of end-of-period shareholder wealth. Loosely speaking, this objective corresponds to profit maximization. As Poitras (1994) demonstrates, the ethical implications of this objective depend on the future path of common stock prices. While it is tempting to conclude otherwise, it is not even clear if a minimal ethical-is-legal framework can be sustained by a corporation pursuing the goal of SWM.

[2] Some sources also include the medical insurance industry that processes payments for the bulk of medical services, e.g. Conrad (2005). This approach is not adopted in what follows, if only to avoid the difficulties associated with having to assess differences in the profit motive for different types of corporations. In addition, there is considerable variation across countries in the types of insurance companies operating in the medical marketplace. For example, the monopoly medical insurer in Canada is the federal and provincial governments.

[3] In the U.S., the 'institutional review board' (IRB) is also referred to as the 'independent ethics committee' or 'ethical review board'. The purpose of the IRB is to approve, monitor, and review biomedical and behavioral research involving humans. The primary motivation of IRB activities is to protect the rights and welfare of the human subjects involved in the trial. The legislative authority for the IRB can be found in the Food and Drug Administration (FDA) and Department of Health and Human Services (HHS), It is the HHS regulations that specifically empower IRBs to approve, require modifications in (to secure approval), or disapprove R&D clinical trial. IRBs are governed by the Research Act of 1974, Title 45 CFR (Code of Federal Regulations) Part 46. This legislation defines IRBs and requires that IRBs approve all research that receives funding, directly or indirectly, from HHS. Oversight of IRBs resides with the Office for Human Research Protections (OHRP) within HHS. For present

purposes, Title 21 CFR, Part 56 is also important as this requires IRBs oversee clinical trials of drugs involved in new drug applications to the FDA. For Canada, see Canadian Institutes of Health Research et al. (1998).

[4] There were approximately 10,000 children born with severe abnormalities from 1956 to 1961 due to pregnant mothers taking thalidomide, primarily to control morning sickness. While this disaster was an important impetus to imposition of safety testing procedures for new drug approval, there were strong reasons for ethical oversight of medical research activities prior to this date, including the Nazi eugenics experiments and the Tuskegee Syphilis Study (1932–1972) conducted by the U.S. Public Health Service which involved infecting poor, illiterate black men in rural Alabama with syphilis.

[5] 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.

[6] The history of patent protection can be traced to a 1623 act of the English parliament prohibiting monopolies, where an exception of 20 years of monopoly protection was provided to individuals publicly disclosing how the product was produced. In the U.S., a standard utility patent gives its patent owner rights against infringement for up to 21 years from the date of filing an initial patent application. Pharmaceutical companies have developed a range of strategies to extend patent life, such as subsequent patenting for other uses or patenting an improved delivery mechanism.

References

American Medical Association: 2006, *Code of Medical Ethics of the American Medical Association, Current Opinions with Annotations 2006–2007* (American Medical Association, Chicago, IL).

Andersen, M., 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. doi:10.1001/jama.295.23.2759.

Angell, M.: 2004, *The Truth About Drug Companies: How They Deceive Us and What to do About It* (Random House, New York).

Avorn, J.: 2006, '"Dangerous Deception" Hiding the Evidence of Adverse Drug Effects', *The New England Journal of Medicine* **355**(November), 2169–2171. doi:10.1056/NEJMp068246.

Berg, C. and K. Fryer-Edwards: 2008, 'The Ethical Challenges of Direct-to-Consumer Genetic Testing', *Journal of Business Ethics* **77**, 17–31. doi:10.1007/s10551-006-9298-8.

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.

Bhandari, M., J. Busse, D. Jackowski, V. Montori, H. Schünemann and S. Sprague, et al.: 2004, 'Association Between Industry Funding and Statistically Significant Pro-Industry Findings in Medical and Surgical Randomized Trials', *Canadian Medical Association Journal* **170**, 477–480.

Campbell, E.: 2007, 'Doctors and Drug Companies: Scrutinizing Influential Relationships', *The New England Journal of Medicine* **357**(November), 1796–1797. doi:10.1056/NEJMp078141.

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada: 1998, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*. 1998 (with 2000, 2002, 2005 Amendments).

Caplovitz, A.: 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.

Chew, L., 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. doi:10.1046/j.1525-1497.2000.08014.x.

Conrad, P.: 1992, 'Medicalization and Social Control', *Annual Review of Sociology* **18**, 209–232. doi:10.1146/annurev.so.18.080192.001233.

Conrad, P.: 2005, 'The Shifting Engines of Medicalization', *Journal of Health and Social Behavior* **46**, 3–14.

Conrad, P.: 2007, *The Medicalization of Society* (Johns Hopkins Press, Baltimore, MD).

Conrad, P. and V. Leiter: 2004, 'Medicalization, Markets and Consumers', *Journal of Health and Social Behavior* **45**(Supplement), 158–176.

Davidoff, F., B. Haynes, D. Sackett and R. Smith: 1995, 'Evidence-Based Medicine: A New Journal to Help Doctors Identify the Information They Need', *British Medical Journal* **310**, 1085–1086.

Davis, J.: 2006, 'How Medicalization Lost Its Way', *Society* **43**, 51–56. doi:10.1007/BF02698486.

Deshpande, R. and S. El-Chibini: 2005, 'Scientific Marketing Offers a New Way to Get Prescribers', *Canadian Pharmaceutical Marketing* (February), 37–38.

Dhanda, R.: 2002, *Guiding Icarus: Merging Bioethics with Corporate Interests* (Wiley, New York).

Donohue J., M. Cevasco and M. Rosenthal: 2007, 'A Decade of Direct-to-Consumer Advertising of Prescription Drugs', *New England Journal of Medicine* **357**(7), 673–681.

Eaton, M.: 2004, *Ethics and the Business of Bioscience* (Stanford University Press, Stanford, CA).

Eaton, M.: 2008, 'Managing the Risks Associated with Using Biomedical Ethics Advice', *Journal of Business Ethics* **77**, 99–109. doi:10.1007/s10551-006-9296-x.

Freidson, E.: 1970, *Profession of Medicine* (Dodd, Mead, New York).

Greene, J.: 2004, 'Attention to ''Details'': Etiquette and the Pharmaceutical Salesmen in Postwar, USA', *Social Studies of Science* **34**, 271–292. doi:10.1177/0306312704043029.

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

Healy, D.: 2004, 'Shaping the Intimate: Influences on the Experience of Everyday Nerves', *Social Studies of Science* **34**, 219–245. doi:10.1177/0306312704042620.

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', *The American Journal of Psychiatry* **194**, 185–194.

Jones, D.: 2007, 'Health Authority Bans Physician Shadowing', *Canadian Medical Association Journal* **177**, 1339–1340. doi:10.1503/cmaj.071572.

Jones, G. and R. Hagtvedt: 2008, 'Marketing in Heterozygous Advantage', *Journal of Business Ethics* **77**, 85–87. doi:10.1007/s10551-006-9301-4.

Lynch, M.: 2004, 'Ghost Writing and Other Matters', *Social Studies of Science* **34**, 147–148. doi:10.1177/0306312704044964.

McGee, G.: 2003, *Pragmatic Bioethics* (MIT Press, Cambridge, MA).

Meredith, L.: 2000, 'Strategic Choices for Business Marketers', in S. B. Dahiya (ed.), *The Current State of Business Disciplines, Vol. 6: Marketing* (Spellbound Publications, Rohtak, India), pp. 2909–2919.

Moynihan, R. and A. Cassels: 2005, *Selling Sickness: How the World's Biggest Pharmaceutical Companies are Turning Us All into Patients* (Greystone Books, Vancouver).

O'Neil, P.: 2008, 'Ethics Guidelines for Clinical Trials to be Revised', *Canadian Medical Association Journal* **178**(2), 138. doi:10.1503/cmaj.071748.

Parsons, T.: 1951, *The Social System* (Free Press, Glencoe, IL).

Poitras, G.: 1994, 'Shareholder Wealth Maximization, Business Ethics and Social Responsibility', *Journal of Business Ethics* **13**, 125–134. doi:10.1007/BF00881581.

Radley, D., S. Finkelstein and R. Stafford: 2006, 'Off-Label Prescribing Among Office Based Physicians', *Archives of Internal Medicine* **166**, 1021–1026. doi:10.1001/archinte.166.9.1021.

Robbins-Roth, C.: 2000, *From Alchemy to IPO: The Business of Biotechnology* (Perseus, Cambridge, MA).

Schafer, A.: 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.

Sismondo, S.: 2004, 'Pharmaceutical Maneuvers', *Social Studies of Science* **34**, 149–159. doi:10.1177/0306312704042575.

Steinman, M., 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**, 284–293.

Szasz, T.: 1958a, 'Psychiatry, Ethics, and the Criminal Law', *Columbia Law Review* **58**(February), 183–198. doi:10.2307/1119827.

Szasz, T.: 1958b, 'Scientific Method and Social Role in Medicine and Psychiatry', *A.M.A. Archives of Internal Medicine* **101**(February), 228–238.

Szasz, T.: 1961, *The Myth of Mental Illness* (Harper and Row, New York).

Thompson, J., 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* (J. Lorimer, Toronto).

Turner, E., A. Matthews, E. Linardatos, R. Tell and R. Rosenthal: 2008, 'Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy', *The New England Journal of Medicine* **358**, 252–260. doi:10.1056/NEJMsa065779.

United States National Institutes of Health: 2008, 'ClinicalTrials.gov Website', http://clinicaltrials.gov/ct2/search/map.

Wootton, B.: 1959, *Social Science and Social Pathology* (Assisted by V. G. Seal and R. Chambers) (Macmillan, New York).

Zola, I.: 1972, 'Medicine as a Institution of Social Control', *The Sociological Review* **20**, 487–504.

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