Court File No. OS-CV-303001PD2

ONTARIO
SUPERIOR COURT OF JUSTICE

BETWEEN:

CANWEST MEDIAWORKS INC.

Applicant

- and -

ATTORNEY GENERAL OF CANADA

Respondent

AFFIDAVIT OF DR. JOHN ABRAMSON
(sworn May 7, 2007)

I, Dr. John Abramson, of the Town of Ipswich, in the State of Massachusetts, in the United States of America, AFFIRM THAT:

1. I am a medical doctor licensed to practice medicine in the state of Massachusetts since 1982. I have been Board Certified in Family Medicine and a Diplomate of the American Board of Family Practice since 1982. I graduated cum laude from Harvard College in 1970 with a degree in Social Relations. I attended Dartmouth Medical School and graduated with a degree in Medicine from Brown Medical School in 1976. I have served as Chair of the Department of Family Practice at Lahey Clinic in Burlington Massachusetts from 1994-2001, and been a clinical instructor at Harvard Medical School since 1997. I am currently also the Executive Director of Health Management Wells Fargo Health Solutions. A copy of my Curriculum Vitae is attached as Exhibit "A" to this affidavit.

2. The issue of public health and health policy and how doctors process information from various sources has been of importance and interest to me throughout my career as a physician. Because of the changes that I was observing in American medicine and experiencing in my own

practice, I left clinical practice to devote full time to research this topic, specifically in regard to the pharmaceutical industry and its impact on public health, public safety, and the quality of American health care. Since the beginning of 2002 I have been researching, writing, lecturing, and teaching about how the information and misinformation about drugs and other medical products available to practicing physicians impacts their medical decisions and the overall quality, effectiveness, and cost of American health care.

3. My involvement with and expertise in women's health issues is from both clinical and research perspectives. I practiced as a family physician for more than 22 years. During this time I provided primary care to women of all ages, including routine GYN care, contraception, and treatment of menopausal symptoms, as well as providing general primary care services to women of all ages. As a researcher, I included chapters and or sections about Hormone Replacement Therapy, cholesterol-lowering therapy, and the diagnosis and treatment of osteoporosis in "Overdosed America" (HarperCollins, 2004). I have collaborated with Judy Norsigian, executive director of Our Bodies, Our Selves, and her colleagues in the chapter on heart disease prevention in the book on Menopause. I co-authored a commentary in the Lancet about the lack of evidence supporting the recommendations for treatment of women and people over the age of 70 with statins for the primary prevention of heart disease.

4. I have been retained by the Canadian Health Coalition, the Canadian Federation of Nurses Unions, Women and Health Protection, the Communications, Energy and Paperworkers Union of Canada, the Canadian Union of Public Employees, Terence Young, the Society for Diabetic Rights and the Medical Reform Group, for the purposes of commenting on the potential consequences of removing or otherwise weakening Canadian regulatory controls over direct to consumer advertising (DTCA) of prescription drugs, as these affect women and women's health. It is for this purpose, and on the basis of my education, training, two decades of clinical practice and my independent research, that I offer the evidence and opinions set out below.

5. As my evidence indicates, my experience is primarily with the U.S. system of drug regulation and promotion. Where the evidence I refer to includes studies or analysis of the

Canadian system, that is so noted. However there are several reasons to conclude that the observations and evidence related below apply to a large extent to Canada as well. First, the drug industry in both countries is dominated by the same international conglomerates that deploy similar strategies whether in the U.S, Canada or Europe – as the journal articles published abroad, and referred to throughout my evidence, attest. Second, the medical research and publishing industries in both countries are closely inter-related and Canadian physicians and policy makers routinely refer to US publications such as the Journal of American Medical Association and the New England Journal of Medicine as authoritative sources. Third, the approach to drug approvals and regulation in both countries has many common features, suffers in a similar way from public funding constraints, and is similarly vulnerable to regulatory capture by the drug industry. The important point is that the resources, strategies and tactics of the drug industry are deployed wherever their products are marketed, and while these will adjust to the particular cultural and regulatory environments of a particular jurisdiction, the observations I make about the influence of this industry over research, publishing, and the regulatory system is much the same in the U.S., Canada and abroad.

6. For present purposes, the most significant difference between Canada and United States is that in Canada, far narrower scope for DTCA is permitted. Because of the similarities of our respective policies and regulations in other respects, the U.S. therefore provides a good case study of the consequences that are likely to follow from allowing greater opportunities for DTCA in Canada. It might be argued in response that effective regulatory control is the answer to the demonstrable problems, described below, that DTCA presents. For this reason I have described the US regulatory system as it pertains to drug approvals and marketing in some detail to make the point that even robust and sophisticated regulatory regimes have not been sufficient or reliable to protect the public from the harms that DTCA can and has caused. This is further borne out by Canadian experience, because as one of case studies included below shows, the drug industry has found ways to exploit even limited advertising opportunities to convey misleading and harmful information about drugs, in this particular case to young women.

7. Furthermore, the issue of DTCA must be viewed in context, and in particular with an understanding of the impacts that have followed from the increasing control that pharmaceutical companies have gained over medical research, publishing and education over the past two decades. These developments have allowed the pharmaceutical industry to exert a pervasive influence over most sources of information concerning the efficacy and risks associated with the use of prescription drugs. This in turn has undermined the ability of physicians to access independent and reliable information about these products in order to make the best decisions for their patients. The inherent problems associated with the deficiencies and weaknesses of the scientific information concerning prescriptions drugs are further compounded when information is conveyed directly to patients who are far less knowledgeable about, or able to critically assess information about the benefits and risks associated with taking prescription drugs. My research as well as my experience in clinical practice both lead to the conclusion that there is a synergistic effect between the commercialization of the information available to prescribers and the inflated demand for expensive new prescription drugs created by product-claim direct to consumer advertising.

8. DTCA must be understood in the context of the totality of the other promotional activities engaged in by pharmaceutical companies. These involve a very substantial commitment of corporate resources and diverse strategies that target health care professionals, regulators, and policy makers in addition to consumers, and are often designed to work in concert.

9. With these inter-relationships in mind, the following affidavit is divided into two parts. The first considers the quality of the scientific evidence concerning prescription drugs that is available to medical practitioners, policy makers and consumers. It describes the various ways in which the influence of the pharmaceutical industry has grown and been asserted with respect to clinical decisions that physicians must make. The second begins with some general observations about the impacts of DTCA in light of the weaknesses and deficiencies of the scientific foundation for assessing the efficacy and risks associated with the use of prescription drugs, and in light of the other promotional activities carried out by the pharmaceutical industry. When the sale of a drug is promoted and the risks of use are unknown or poorly understood, serious harm

may result to those exposed. However my primary focus is on the particular problems these realities create for women because of various factors related to sex and gender. In this regard, a number of case studies are presented that illustrate the particular risks and harm associated with DTCA for women's health. As this evidence and analysis indicates, a weakening of present Canadian regulatory controls of DTCA is likely to result in problems similar to those that can be observed in jurisdictions that have allowed greater scope for such advertising, namely the U.S. and New Zealand (which has recently reinstated regulatory controls), and exacerbate problems related to informational drug advertising, which can already be observed in Canada notwithstanding the more limited scope for such advertising. While these impacts are serious for all consumers, they present particular and often more serious consequences for women for several reasons, including their own reproductive health needs which bring them into greater contact with medical care; their care-giving roles in the family which often require them to make healthcare decisions for their children and other relatives; and their longer life spans which lead to greater exposure to medicines for chronic diseases. As well, women's magazines are often filled with multiple drug ads, while advertising in the general media tends to be more focussed on drugs that women are more likely to take. Finally, testing and approvals protocols for new drugs often fail to identify or obscure risks that may be particular for women, therefore exposing them to greater or unknown risks, as the evidence arising from the withdrawals of certain drugs from the market indicates.

PART I: THE QUALITY OF THE SCIENTIFIC EVIDENCE ABOUT BRAND NAME DRUGS AVAILABLE TO MEDICAL DECISION MAKERS

How are Standards of Care Established?

10. Doctors, various health care health care officials, both public and private insurers, and policy makers rely upon several common sources of information about the safety and efficacy of prescription drugs. For present purposes the most important of these are:

- Original research and review articles published in peer-reviewed journals – the primary source of medical information for practicing physicians. The medical

"literature" defines the scientific evidence that provides the foundation for "evidence-based medicine."

- Clinical Practice Guidelines (CPGs) – are typically formulated by panels of experts under the auspices of medical professional societies (like the American Psychiatric Association), non-profit organizations (like the American Heart Association), and quasi-governmental organizations (like the National Cholesterol Education Program under the auspices of the National Institutes of Health/National Heart, Lung, and Blood Institute). In Canada, similar guidelines are promulgated under the auspices of organizations such as the Canadian Psychiatric Association, the Heart and Stroke Foundation of Canada, and the Canadian Cardiovascular Society (cholesterol guidelines). CPGs play an important role in defining the standards of good medical care. [1], [2]

- Continuing Medical Education (CME) – Doctors also keep abreast of developments in their field through continuing medical education, which plays a major role in doctors' fulfillment of the responsibility to their patients to stay current with new medical knowledge. These educational programs are typically provided by recognized clinical experts, referred to as "thought leaders" or "key opinion leaders," often recognized and virtually always respected by practicing physicians.

- Marketing and Drug Reps – In the U.S. the number of drug reps making sales calls in doctors' offices tripled between the early 1990s and 2001, and now there are about 90,000 drug reps making calls on practicing physicians, or one full time

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[1] Choudhry NK, Stelfox HT, Detsky AS, Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry, *JAMA,* 2002;287:612-17.

[2] Grilli R, Magrini N, Penna A, et al, Practice guidelines developed by specialty societies: the need for a critical appraisal, *Lancet,* 200;355:103-06.

rep for every four and half office based doctors.[3] While these statistics vary somewhat for Canada, the same trends have occurred there as well.[4]

- Public Relations and Non-profit Public Service Organizations – A major source of medical information for both consumers and medical providers is trusted non-profit organizations like the American Heart Association, the National Osteoporosis Foundation, the Arthritis Foundation, and the National Alliance of the Mentally Ill, to name just a few.

- Formulary Decisions / Cost Effectiveness Data – Physicians tend to prescribe drugs that are covered on the formularies of managed care organizations, pharmacy benefit management companies, or public payers such as Medicaid, Medicare or provincial drug plans in Canada.

- The U.S. Food and Drug Administration - The FDA's primary responsibility is to ensure the safety and efficacy of new drugs prior to approval and to monitor ongoing safety issues in drugs that are already on the market. New prescription drugs are not approved by the FDA for use in general, but only for the specific diseases or conditions for which the FDA has determined the drug to be safe and effective. The FDA works with drug makers to develop an FDA-approved product label that reflects the indications for use and dosages that the FDA has determined to be safe and effective. The FDA only approves a new drug application if the labelling is consistent with FDA-approved uses and dosages, and drugs can only be marketed in the United States for the indications that have been approved by the FDA. I am advised by Counsel that analogous regulatory

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[3] Scott Hensley, "As Drug-Sales Teams Multiply, Doctors Start to Tune Them Out", *Wall Street Journal,* June 13, 2003.

[4] Based on companies that consecutively reported detailing staff, 1998-2002. IMS Health Canada's 2002 Detailing Survey.

functions are carried out in Canada primarily by various directorates operating under the auspices of the Health Products and Food Branch of Health Canada.[5]

- The Office of Drug Safety (now renamed as the Office of Surveillance and Epidemiology, OSE) has ongoing responsibility for overseeing the safety of drugs after they are approved. These responsibilities include updating drug labelling, developing a risk management program when problems or potential problems are identified, and occasionally "re-evaluating approval or marketing decisions." [6] I am advised by counsel that in Canada some of these responsibilities have been assigned to the Marketed Health Products Directorate while others are carried out under other Directorates of Health Canada, and by the Public Health Agency of Canada.

- The FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) oversees the marketing and promotion of FDA-approved drugs to ensure that manufacturers do not make false or misleading claims in drug marketing and that manufacturers do not promote a drug for uses that are not FDA-approved.

- Public policy makers – Public policy concerning medical issues relies upon the best available scientific evidence:

> Applied medical research creates the evidence-based target. The health policy enterprise rightfully focuses on this standard as a guide to health care improvement and reform.[7]

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[5] Health Canada: *Overview of the Canadian Federal Drug Review Process*; http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/overview-apercu_drug-med_rev_pro_03_07_e.html

[6] Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, FDA. http://www.fda.gov/CDER/Offices/ODS/default.htm accessed 1/27/07.

[7] Spitz B, Abramson J, When Health Policy is the Problem: A Report from the Field, *Journal of Health Politics, Policy and Law*, 2005;30:327-65.

The Influence of Pharmaceutical Companies Over Various Sources of Information About the Safety and Efficacy of Prescription Drugs

A. Original Research

11. Physicians rely on the findings of original research studies published in respected peer-reviewed medical journals in order to make the best decisions for their patients. However, corporate influence now permeates virtually every aspect of this process from the design of clinical studies (including the population included in the trial, choice of drugs, doses, and duration of the trial, and outcome and safety measures to be tracked); control of the data and data analysis; to the writing of manuscripts for articles and publishing decisions. This has created a danger to patients, as results of clinical trials can be "spun" to favor the interests of corporate sponsors, exaggerating benefits and minimizing adverse events.

1. The Growing Dependence of Academic Centers on Commercial Sources of Research Funding

12. As the National Institute of Health ("NIH") funding of clinical trials started decreasing in the late 1970s, pharmaceutical companies moved in to fill the void. Between 1977 and 1990 pharmaceutical companies increased their funding for clinical trials 6-fold.[8] By 1991, approximately 70% of clinical trials were being funded by the pharmaceutical companies, but 80% of those trials were still being carried out in academic medical centers where there was a tradition of academic researchers participating in study design, data analysis, and publication

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[8] Dramatic Growth of Research and Development, Pharmaceutical Research and Manufacturers of America (PhRMA), *Pharmaceutical Industry Profile 2003* (Washington , DC: PhRMA, 2003). http://www.phrma.org/publications/publications/profile02/2003%20CHAPTER%202.pdf accessed 2/14/03.

decisions.[9] As the 1990s progressed, this changed dramatically, so that by 2000 only 41% of commercially funded studies were being done in universities - the rest were being done by for-profit contract research organizations. And by 2004, only 26% of commercially funded studies were being performed in an academic setting.[10] I am unaware of any similar Canadian data to track such trends; however in Canada between 1997 and 2004 the percent of trials in the community went up from 47% to 60% of the total.[11]

13. There is nothing inherently unethical about this change in the locale. It allows the drug companies to get their research done with less red tape, more quickly, and with lower overhead. But one important consequence of this transition is that it changed the locus of control of clinical research from academic researchers working in academic medical centers to the pharmaceutical companies themselves. Since pharmaceutical companies were hiring the research companies directly, they could play the primary role in designing the study and controlling the data, while at the same time denying researchers, who are to author the articles published in medical journals (the "scientific evidence") free access to the data. This allows the pharmaceutical companies to retain a great deal of control over publication decisions. Currently, 70- 80% of clinical research is now commercially funded.[12] In the 10 years between 1994 and 2003, 65 of the 77 most frequently cited clinical trials (84 percent) had commercial sponsorship. Furthermore, the percentage increased significantly during that time and since 1999, 31 out of 32 of the most frequently cited clinical trials (97 percent) had industry sponsorship.[13]

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[9] Bodenheimer T. Uneasy alliance – clinical investigators and the pharmaceutical industry. *New England Journal of Medicine.* 2000;342:1539-1544.

[10] Steinbrook R, Gag Clauses in Clinical-Trial Agreements, *NEJM,* 2005;352:2160-62.

[11] Silversides A. The tribulations of community-based trials. CMAJ 2004;170:33.

[12] In 2002 70% of funding in U.S. came from biopharmaceutical industry & 10% from device manufacturers (Getz K. Clinical grants market decelerates. *Centerwatch.* 2003;10(4):1-6.)

[13] Patsopoulos NA, Ionnidis JPA, Analatos AA, Origin and funding of the most frequently cited papers in medicine : database analysis, *BMJ* 2006;332;1061-1064.

14. A study published in the New England Journal of Medicine ("NEJM") examined the standards for the 25% of clinical trial contracting agreements that should be maintaining the highest standards of academic independence – the arrangements between pharmaceutical companies and academic medical centers. The researchers found that more than two-thirds of the academic institutions accepted research contracts that prohibit researchers from changing the sponsor's research design. Half of the university medical centers allowed commercial sponsors to "draft manuscripts reporting the research results, with the investigators' role limited to review and suggestions for revision." And "24 percent of the responding institutions would grant the sponsor the right to insert its own statistical analyses into manuscripts." This among the one-quarter of commercially-sponsored research contracts that should be preserving the greatest scientific independence.[14]

15. Discussing the failure of universities to defend their scientists' research independence when doing commercially-sponsored medical studies, Drummond Rennie, MD, Journal of the American Medical Association Deputy Editor, said that universities and scientists "are seduced by industry funding, and frightened that if they don't go along with these gag orders, the money will go to less rigorous institutions...It's a race to the ethical bottom."[15] Given the primary fiduciary responsibility of the drug companies to their shareholders rather than the public's health, this transition from public to private financing of clinical research means that – at best – studies will be designed and our medical knowledge will grow towards maximizing corporate profits rather than optimizing health most effectively and efficiently.

16. Thirteen editors of the world's most prestigious medical journals, including the Canadian Medical Association Journal, issued an alarming joint statement highlighting the extent and consequences of the commercial takeover of clinical research. In the report they stated:

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[14] Mello MM, Clarridge BR, Studdert DM, Academic medical centers' standards for clinical-trial agreements with industry, *N Engl J Med*, 2005;352:2202-10.

[15] Knox RA. Boston Globe, March 30, 1999

> "Until recently, academic, independent clinical investigators were key players in design, patient recruitment, and data interpretation in clinical trials. The intellectual and working home of these investigators, the academic medical center, has been at the hub of this enterprise, and many institutions have developed complex infrastructures devoted to the design and conduct of clinical trials. But, as economic pressures mount, this may be a thing of the past.
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> Investigators may have little or no input into trial design, no access to the raw data, and limited participation in data interpretation. These terms are draconian for self-respecting scientists, but many have accepted them because they know that if they do not, the sponsor will find someone else who will."[16]

17. Between two-thirds and three-quarters of the clinical studies published in even the most prestigious journals are now commercially funded.[17] Among the highest quality studies (those deemed good enough to be included in Cochrane Reviews), the odds are 5.3 times greater that commercially funded studies will conclude that the sponsor's drug is the treatment of choice compared to non-commercially funded studies of exactly the same drugs.[18] This means that the "scientific evidence" produced by commercially sponsored studies is effectively and systematically biased in favor of the sponsor's drug. An editorial in the American Journal of Medicine noted that the "link between commercial sponsorship and the conduct and presentation of research" is difficult to minimize "because there is usually a substantial power gradient between the sponsor and the investigator."[19]

18. A rare window into the problem of authors of commercially sponsored research not having access to the data from their own study was provided by the 11 non-Merck employees' (including the lead author) response to the "Expression of Concern" issued by the editors of the

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[16] Davidoff F, DeAngelis DC, Drazen JM, et al. Sponsorship, Authorship, and Accountability, *N Engl J Med,* 2001; 345: 825-7.

[17] Smith R, Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies, *PLOS Medicine,* 2005; 2(5):e138 DOI: 10.1371/journal.pmed.0020138

[18] Als-Neilsen B, Chen W, Gluud C, Kiaergard LL, Association of Funding and Conclusions in Randomized Drug Trails, *JAMA,* 2003; 290:921-928.

[19] Landefeld CS, Commercial Support and Bias in Pharmaceutical Research, *Am J Med,* 2004;117:876-8.

NEJM[20] about three heart attacks that occurred in the Vioxx Gastrointestinal Outcomes Research ("VIGOR") trial that were not included in the Nov. 23, 2000 NEJM article reporting the results. The non-Merck employed authors wrote:

> These events were neither in the locked database used in the analysis for the VIGOR paper nor known to us during the review process.[21]

In other words, the non-Merck employee authors of the VIGOR article published in the New England Journal of Medicine – including the lead author – were not aware of the occurrence of the additional three heart attacks, and therefore did not have the opportunity to participate in the decision about whether or not to include them in the paper which they authored. That the NEJM editors' rejected the authors' justification for not including the three heart attacks in the paper[22] is not the important point here. Rather, of the 13 authors of the paper, only the two employed by Merck were given the opportunity to participate in the decision about how to handle the crucial statistical ramifications that the additional three heart attacks posed. The other authors were deprived of the opportunity to participate in this crucial decision about the data in the paper they authored. (This omission of critical data is particularly relevant to the issue of DTCA: The same year that the NEJM article that presented the incomplete results of the VIGOR trial, Vioxx was the most heavily advertised drug to consumers (see below).)

2. Commercial Control of Scientific Articles Published in Peer-Reviewed Journals

19. Drug manufacturers can also bias even the most trusted "scientific evidence" by having financial relationships with researchers, funding research, and coordinating research

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[20] Curfman GD, Morrissey S, Drazen JM, Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Refecoxib and Naproxen in Patients with Rheumatoid Arthritis," N Engl J Med 2000;343:1520-8. *NEJM,* 2005;353:2813-4.

[21] Bombardier C, Laine L, Burgos-Vargas R, et al, Response to Expression of Concern Regarding VIGOR Study, *NEJM,*2006;354:1196-8.

[22] Curfman Gd. Morrisey S, Drazen JM, Expression of Concern Reaffirmed, N Eng J Med, 2006;354:1193.

publications. A study of the effect of researchers' financial conflicts of interest and industry funding on clinical trials, published in the American Journal of Psychiatry in 2005, concluded: "Industry sponsorship and author conflict of interest are prevalent and do appear to affect study outcomes."[23] The study looked at clinical trials that were published between 2001 and 2003 in the four most widely cited general psychiatry journals. Forty-seven percent of the articles included at least one author with a financial conflict of interest, defined as "any report of consulting or speaking fees or honoraria, stock ownership, or employment by the study sponsor." The odds were 4.9 times higher that articles with at least one author having a conflict of interest would report positive results for the drug company's product. For those studies that had both industry sponsorship and at least one author with a conflict of interest the odds were 8.4 times higher that the study would favor the sponsor's drug ($p<0.001$ for both odds ratios).

20. An example of the effect of commercial coordination of research publications can be found in a 2003 article in the British Journal of Psychiatry showing the effect of such coordination on the publications concerning the antidepressant Zoloft between 1998 and 2001.[24] Fifty-five out of a total of 96 articles published during this interval were coordinated by Current Medical Directions ("CMD"). CMD is a medical information company hired by Pfizer, the manufacturer of Zoloft. The raw data from the research presented in these articles was, "in almost all instances," proprietary—meaning that the authors often did not have free access to the untabulated data, and if they did, were not free to share the data with colleagues. These 55 articles included, according to the article in the British Journal of Psychiatry,

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[23] Perlis RH, Perlis CS, Wu Y, et al, Industry Sponsorship and Financial Conflict of Interest in the Reporting of Clinical Trials in Psychiatry, *Am J Psychiatry,* 2005;162:1957-1060

[24] Healy D, Cattell D, Interface between authorship, industry and science in the domain of therapeutics, *Br J Psych,* 2003; 183:22-27.

> "a number of publications that the document suggests originated within communication agencies, with the first draft of articles already written and the authors' names listed as 'to be determined.'"[25]

21. In other words, these articles were ghostwritten for the authors whose names later appeared on the published articles. Readers are not always informed about these relationships: only two of the 55 articles followed current medical journal guidelines by acknowledging "writing support from individuals not listed as authors." In addition, readers of the articles often are not aware of authors' financial ties to the drug maker:

> "Of the published articles, 13 of the 55 do not appear to have a company author or to have been through an agency. Four of these 13 articles involved economic models based on data provided by Pfizer, and it is assumed that these authors do not have access to raw data. Five of the 13 are review articles appearing in a company-sponsored symposium supplement [to journals]. The remaining four articles acknowledge support funding..."

22. Among the 55 CMD coordinated publications, all of the published clinical and economic analyses were favorable to Zoloft. In contrast, only 18 of the 41 non-CMD coordinated publications reported favorable results. In addition, there is evidence that among the CMD coordinated articles, adverse events were not adequately reported: two of these studies under-report suicide and suicidal behaviors.[26] Finally, CMD-coordinated articles were 5 ½ times more likely to be cited in future articles (and therefore have more impact on what is perceived as the scientific evidence) than the independently published articles ($P \leq 0.001$). This is important because the CMD-coordinated articles are far more likely to be favorable to Zoloft and to have greater impact on the perceived scientific evidence. (Given that anti-depressants are heavily advertised to American consumers, the commercial distortion of the what prescribers reasonably believed was the best available "scientific evidence" became even more significant in directing medical care.)

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[25] Ibid.

[26] Ibid (Healy 2003)

23. Commercial bias also plays a role in determining which studies get published and which ones don't, so-called "publication bias." Based upon the six published studies addressing the safety and efficacy of the newer antidepressants in treating depressed children and adolescents, doctors reasonably believed that the scientific evidence clearly showed the benefits of these drugs in treating depression in this population. But the totality of scientific evidence that existed at that point showed just the opposite. In truth there had not been six but fifteen studies completed--nine of which remained unpublished. When all the studies were considered together, the evidence shows that these drugs are not just ineffective for depressed children and adolescents, but also unsafe: doubling the risk of suicidal behavior.[27] In other words, doctors, formulary committees, and policy makers had based their decisions on an unrepresentative fraction of the available scientific evidence. (Even among the six published studies that claimed to have documented effectiveness, three were not confirmed upon independent analysis by British and American regulatory agencies.)[28] NY Attorney General Spitzer sued Glaxo SmithKline, accusing them of publishing one positive study while withholding two negative ones about the safety and efficacy of Paxil in the treatment of depressed children and adolescents. GSK settled for a payment of $2.5 million to the state of New York and denied wrongdoing.

24. Dr. Richard Horton, the current editor of the Lancet, wrote in 2004 (with poetic economy) that the "[medical] journals have devolved into information laundering operations for the drug companies."[29] Publication of an article in a peer reviewed journal is generally taken to mean that unbiased reviewers have deemed the article to reasonable represent the scientific evidence. Doctors are taught to trust the scientific evidence presented in peer reviewed journals. However, their faith in the ability of peer review to assure balanced interpretation of scientific evidence remains unverified as documented by a systematic review of the effect of peer review

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[27] Antidepressant Medications in Children and Adolescents, *Therapeutics Letter,* 2004;Issue 52. http://www.ti.ubc.ca/pages/letter52.htm accessed 1/08/07

[28] Ibid.

[29] Horton R. The dawn of McScience. *New York Rev Books* 2004;51(4):7–9.

published in the Journal of the American Medical Association in 2002. The article concluded: "Editorial peer review, although widely used, is largely untested and its effects are uncertain."[30]

B. Review Articles

25. The systematic bias in the results of commercially sponsored clinical trials also appears in commercially sponsored review articles. An article published in the British Medical Journal compared the quality and results of commercially-sponsored reviews (meta-analyses) comparing two drugs to Cochrane reviews (non-commercial, highest quality) of the same design, as well as to those with undeclared support and those with non-commercial support. The study found that the estimated treatment effects of the drugs being reviewed were reported to be the same in the commercially sponsored reviews and Cochrane reviews (as would be expected because of the unambiguous nature of the results that are reported). However, the effect of commercial sponsorship was revealed in the recommendations that then followed:

> "The estimated treatment effects in industry supported reviews were similar to those of Cochrane reviews, but the former had uniformly positive recommendations for the experimental drug, without reservations about methodological limitations of the trials or costs, in contrast to none of the Cochrane reviews. This suggests that the main problem with industry supported reviews lies in how conclusions are formulated."[31]

C. Clinical Practice Guidelines

26. Ironically, studies of the quality of clinical practice guidelines show that they often don't meet accepted standards. One study, aptly titled "Are Guidelines Following Guidelines?" published in JAMA in 1999 concluded that:

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[30] Jefferson T, Alderson P, Wagner E, Davidoff F, Effects of Editorial Peer Review, *JAMA,* 2002;287:2784-86.

[31] Jorgensen AW, Hilden J, Gotzsche PC, Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review, *Br Med J,* 2006 Oct 14;333(7572):782. Epub 2006 Oct 6. Review.

> "Guidelines published in the peer-reviewed medical literature during the past decade do not adhere well to established methodological standards. While all areas of guideline development need improvement, greatest improvement is needed in the identification, evaluation, and synthesis of the scientific evidence".[32]

27. Another study of the quality of clinical practice guidelines found that only 6 out of 33 guidelines established (in this particular study) for the treatment of hypertension and hyperlipidemia fulfilled at least 5 of 8 established methodological standards, that guidelines issued by specialty societies were less likely to fulfill accepted standards, and that the guidelines that did not adhere to accepted standards were more likely to recommend more aggressive treatment (initiation of treatment at lower thresholds and/or the use of higher doses of drugs).[33] In 2000, The Lancet published a report that found that only one out of twenty guidelines met established standards of quality for three simple criteria: description of the professionals involved in formulating the guidelines; description of the sources of information used to find the relevant scientific evidence; and grading of the evidence used to support the main recommendations.[34]

28. In 2002, a study published in JAMA showed that four out of five experts who participate in the formulation of clinical practice guidelines have financial relationships with drug companies, averaging more than ten such relationships each. And 59 percent of these experts "had relationships with companies whose drugs were considered in the guideline they authored." Would we tolerate a judge having ongoing financial relationship with one of the litigants in a case he or she was hearing? Nonetheless, more than half of the guidelines (both from the U.S.

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[32]Shaneyfelt TM, Mayo-Smith MF, Rothwangl J, Are Guidelines Following Guidelines:: The Methodological Quality of Clinical Practice Guidelines in the Peer-Reviewed Medical Literature, *JAMA*, 1999;281:1900-1905.

[33] Fretheim A, Williams JW, Oxman AD, Herrin J, The relation between methods and recommendations in clinical practice guidelines for hypertension and hyperlipidemia, *J of Fam Practice,* 2002;51:963-8.

[34] Grilli R, Magrini N, Penna A, et al. Practice Guidelines Developed by Specialty Societies: The Need For a Critical Appraisal. *The Lancet.* 2000:3555:103-06.

and Canada) included in this JAMA study had been subject to no formal standard or process for declaring participants' relationships with drug companies. [35]

D. Continuing Medical Education

29. Commercial sponsorship of doctors' continuing medical education has been increasing rapidly: from approximately $400 million in 1998 to approximately $700 million in 2001.[36] Commercial funding of CME activity grew from 48 percent in 1998 to 58 percent in 2002.[37] And in 2002, the commercial investment in doctors' CME increased by another 30 percent. [38] In 2005, 60 percent of doctors' continuing education was funded directly by the drug and medical device industries. Additional funding was provided by non-profit organizations, which may have been funded by commercial interests, but are not included in the 60 percent due to a change in the Accreditation Council for Continuing Medical Education's changed definition of "commercial support."[39] Total industry contribution of doctors' continuing medical education has been estimated to be 70 percent or higher.

30. According to the past president the Pharmaceutical Research and Manufacturers of America (PhRMA):

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[35] Choudhry NK, Stelfox HT, Detsky AS, Relationships between authors of clinical practice guidelines and the pharmaceutical industry, *JAMA,* 2002;287:612-17.

[36] Hensley S, When Doctors Go to Class, Industry Often Foots the Bill, *Wall Street Journal,* December 4, 2002.

[37] Op. Cit. Harrison

[38] Relman A, Industry Sponsorship of Continuing Medical Education Reply to Letters, *JAMA,* 2003;290:1150

[39] Croasdale M, More dollars flow into continuing medical education, American Medical News (American Medical Association), August 21, 2006. http://www.ama-assn.org/amednews/site/free/prsb0821.htm#s1 accessed 12/24/06.

> **Industry-supported conferences, seminars, and symposia are helping physicians to provide the best, most appropriate, and most up-to-date health care to their patients. They help to ensure the widespread adoption of new medicines and technologies that save lives, cure disease, relieve pain, and allow individuals to lead longer, healthier, and more productive lives.[40]**

31. All that said by PhRMA, drug companies base their ongoing support of continuing medical education on increased use of their own products.[41]

32. A review article published in JAMA shows that drug company-sponsored lectures are two-and-a-half to three times more likely to mention the sponsors' drug in a positive light and the competitors' drugs in a neutral or negative light than are non-commercially sponsored lectures.[42] Furthermore, the odds are 3.9 times greater that doctors who accepted money from drug companies for speaking at CME activities would make specific requests for addition of the sponsor's drug to the hospital formulary.[43]

33. At least as important as favoring the sponsor's drug, the growing commercial funding of continuing medical education influences the curriculum topics that are addressed.[44] Commercially funded education is more likely to be about the kinds of new information that has maximum potential to increase the sponsor's profits rather than maximizing patients' health.

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[40] Holmer AF. Industry strongly supports continuing medical education. *Journal of the American Medical Association* 2001;285:2012-2014.

[41] Brennan TA, Rothman DJ, Blank L, et al. Health Industry Practices that Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers, *JAMA*, 2006;295:429-433.

[42] Wazana A. Physicians and the pharmaceutical industry. *JAMA*, 2000;283:373-380

[43] Chren M-M, Landefield CS. Physicians' Behavior and Their Interactions With Drug Companies: A Controlled Study of Physicians Who Requested Additions To a Hospital Drug Formulary. *JAMA*. 1994;271:684-689.

[44] Op. Cit. Harrison

E. Drug Reps

34. A common site in doctors' offices are pharmaceutical sales representatives, commonly known as the "drug rep", bearing free samples, gifts, often lunch, and the latest information regarding their drug. Though most doctors find the information presented by drug reps both useful and accurate (see above), an article published in the Journal of General Internal Medicine shows that nearly half (42%) of the material given to doctors by drug reps made claims in violations of FDA regulations. And only 39% of the material provided by drug reps provided scientific evidence to back up claims.[45] A review published in JAMA shows mostly a negative effect on the quality of care of doctors' interactions with drug companies and drug reps.[46]

35. For example, the more interactions with pharmaceutical company marketing people, drug samples in hand, the greater the likelihood that doctors will prescribe newer, more expensive drugs and fewer generic drugs. The more a doctor sees drug reps, the less likely the doctor is to identify false claims about the drug and the greater the doctor's tendency to prescribe more drugs overall. The odds are 15 times greater that doctors who interact with drug companies will request that drugs manufactured by a specific company be included in hospital formularies.[47]

F. Public Relations and Non-Profit Organizations

36. While the sponsor of advertising aimed at consumers and prescribers is usually identified, sponsorship of public relations campaigns is more difficult, if not impossible, to spot.

37. For example, prior to the FDA's approval of Paxil for the treatment of "social anxiety disorder" ("SAD"), this affliction had been, according to the psychiatric diagnostic manual,

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[45] Stryer D, Bero LA, Characteristics of Materials Distributed by Drug Companies: An Evaluation of Appropriateness, *Journal of General Internal Medicine*, 1996;11:575-583.

[46] Op. Cit. Wazna

[47] Ibid

"extremely rare." The rarity of social anxiety disorder quickly became a thing of the past after SmithKline Beecham hired a public relations firm to conduct an "educational" campaign, with the support of three non-profit organizations: the American Psychiatric Association, The Anxiety Disorders Association of America, and Freedom From Fear.[48]

> "Increasing public awareness of SAD and other disorders, the consulting firm Decision Resources predicted last year, would expand the "anxiety market" to at least $3 billion by 2009"

38. Another example of an ostensibly non-commercial public education effort is the "Go Red for Women Day," the purpose of which is to increase awareness of women's risk that heart disease is "the #1 killer of women." Although this campaign is ostensibly sponsored by the National Heart, Lung, and Blood Institute, there are "other corporate sponsors." They would be Pfizer and Macy's. In truth, below the age of 75 cancer takes the lives of 78 percent more women than does heart disease,[49] and there is no evidence from the gold standard of medical research, randomized controlled trials, that cholesterol-lowering statin drugs (like Pfizer's Lipitor) are beneficial to women who don't already have heart disease.[50]

39. The Attorneys General of 16 states issued a report in April of 1999 expressing concern about the extent to which:

> "commercial-nonprofit product advertisements often communicate the false and misleading messages that the products have been endorsed by the nonprofit partner in the commercial-nonprofit relationship and that such products are superior to other competing products."[51]
>
> The report includes critical examination of commercial relationships with widely respected non-profit organizations including the American Heart Association, the

[48] Kramer B. Disorders Made to Order. *Mother Jones*. July-August 2002.

[49] National Vital Statistics Reports. Centers for Disease Control. 2005:53.

[50] Abramson J, Wright JM. Are lipid-lowering guidelines evidence-based? *Lancet*. 2007;369:168-9.

[51] Bill Lockyer (Attorney General, CA). What's in a Nonprofit's Name. April 6, 1999.

American Cancer Society, the American Diabetes Association, and the American Lung Association.

40. In Canada, the situation is much the same. A study by PriceWaterhouseCoopers details how alliances with non-profit "disease-specific groups" help pharmaceutical companies with market access. Among the advantages that were identified as accruing to the industry, is the ability to promote to new markets, a positive public image through provision of services to the community, and opportunities to "increase their influence with governments through supporting patient advocacy groups". Such activities, they emphasized, would "increase pre-market awareness in targeted patient groups" and establish a "credible vehicle for product information distribution". Patient advocacy groups provided pharmaceutical companies a "bridge to contact with key community leaders who influence national policy, research, drug approval and care delivery".[52]

G. Food and Drug Administration

41. Contrary to common belief, the FDA's responsibilities do not include determining optimal medical practice. Rather their responsibility is limited to approving new drugs based on evidence of safety and efficacy, postmarketing surveillance to ensure drug safety, and oversight of marketing materials to ensure they are consistent with FDA-approved labeling.

1. *New Drug Approval*:

42. FDA approval of a new drug is testimony only the drug's efficacy being superior to placebo, meaning no therapy. Documentation of equivalence or superiority to the best available therapy is not required. Therefore new drugs can be (and are) approved on the basis of Phase III studies showing significantly greater efficacy than placebo that may, nonetheless, be inferior to other therapies already on the market. Determining the clinically most important information—

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[52] Chapman and Rule; *Alliances between disease-specific non-profit organizations and private sector pharmaceutical companies*. PriceWaterhouseCoopers 1999.

where the new drug fits into the spectrum of optimal therapy—is not part of the FDA approval process or responsibility.[53]

43. After the implementation of the Prescription Drug User Fee Agreement the median time for the FDA to approve new drug applications decreased rapidly, and Lexchin describes the same scenario as having played out in Canada.[54]

44. PDUFA increased FDA new drug reviewers' workload, leading the then director of the FDA Center for Drug Evaluation and Research to write in 1994 that the tight deadlines for drug approval were creating "a sweatshop environment that's causing high staffing turnover."[55] A report on CDER done by the Inspector General of the US Department of Health and Human Services found that 58 percent of the medical officers said that the six months allotted for review of priority drugs is not adequate, and that one-third of respondents did not feel comfortable expressing differing opinions.[56]

45. The statistical threshold for safety problems is set at the same level as for efficacy: 95 percent certainty, or in statistical parlance, $p<0.05$. Yet Phase III studies generally are designed for shorter-than-real life use in relatively small-scale studies that are often inadequate to establish the long-term safety of the drug. For example, the Zyprexa label states that "The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials..." and a single study (n=326) that followed patients for a maximum of 8 months. The GAO found that 51 percent of all approved drugs are later found to cause at least one serious

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[53] Ray WA, Stein MB, Reform of Drug Regulation—Beyond an Independent Drug-Safety Board, *NEJM*, 2006;354:194-201.

[54] Lexchin J. Relationship between pharmaceutical company user fees and drug approvals in Canada and Australia: a hypothesis-generating study. Annals of Pharmacotherapy 2006;40:2216-22.

[55] Larry Thompson, "User Fees for Faster Drug Reviews: Are They Helping or Hurting Public Health," *FDA Consumer Magazine*, September-October 2000. http://www.fda.gov/fdac/features/2000/500_pdufa.html accessed 4/1/03

[56] Department of Health and Human Services, Office of Inspector General: FDA's Review Process for New Drug Applications. March, 2003.

adverse drug reaction that was not known at the time of drug approval (i.e. did not appear in pre-approval Phase III studies).[57] It is likely that the experience in Canada would be similar as there is a significant overlap between the Canadian and American market in terms of the drug molecules that are available in the two countries.

46. Two-thirds of commitments for further studies to better establish drug safety made at the time of FDA approval have not been initiated and the FDA lacks the legal authority to enforce these commitments.[58] I am advised by Counsel that Health Canada similarly lacks regulatory authority to require post-marketing trials.

2. *Post Approval Safety*:

47. In 2004, the editors of JAMA made clear the inability of the FDA's postmarketing surveillance system to ensure timely reporting of serious drug safety problems, leaving far greater responsibility upon the drug makers themselves than is generally understood:[59] As noted by Lexchin, the situation is similar in Canada, and Health Canada does not keep a list of drugs that have been withdrawn from the market because of safety problems.

> "The inadequacies of the postmarketing surveillance system (ie, FDA's MedWatch program with passive collection of spontaneous reports of adverse drug reactions) for ensuring safety are well known and include: reliance on voluntary reporting of adverse events by physicians and other health care professionals; poor quality of submitted reports, often with inadequate documentation and detail; underreporting of adverse outcomes with capture of only a small fraction of adverse events that actually occur; difficulty in calculating rates of adverse events because of incomplete numerator data on events, together with unreliable denominator data on exposure; limited ability for spontaneous reports to establish causal relationships; and difficulty in

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[57] Furberg CD, Levin AA, Gross PA, et al, The FDA and Drug Safety: A Proposal for Sweeping Changes, *Arch In Med,* 2006;166:1938-1042.

[58] Furberg Op Cit

[59] Fontanarosa PB, Rennie D, DeAngelis CD, Postmarketing Surveillance—Lack of Vigilance, Lack of Trust, *JAMA,* 2004;292:2647-50.

> determining whether the adverse event resulted from the drug or the disease it was intended to treat."

48. According to the JAMA editors, the major problem with our system of ensuring postmarketing drug safety is that the drug makers themselves are "largely responsible for collecting, evaluating, and reporting data from postmarketing studies of their own products." In addition to the obvious problem of the conflict between the drug makers' and the public's interest (leading to minimization of safety problems), less than half of the postmarketing studies that the drug makers agreed to conduct as condition of approval have not been done.

49. The JAMA editors express concern that the drug manufacturers

> "will continue to use highly defensive articles as well as other tactics, such as threats and attempts at intimidation, to protect their interests and attempt to defend against dissemination of negative information about their products."

50. Another article in JAMA (to which the above editorial refers) used the example of delay in identification of the risk of rhabdomyolysis (severe and potentially fatal breakdown of skeletal muscle) associated with use of cervistatin (Baycol—a cholesterol-lowering statin drug) to point out the slowness of FDA's postmarketing safety-surveillance system:

> "the asymmetry between the information available to the company and the information available to patients and physicians seems striking....under the current system, a pharmaceutical company's appraisal of [suspected adverse drug reactions] may be influenced by economic considerations. Such an appraisal would best be made by an independent group. The US Congress should mandate and provide adequate support for independent reviews and analysis of postmarketing data."[60]

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[60] Psaty BM, Furberg CD, Ray WA, Weiss NSS, Potential for Confl of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cervistatin and Risk of Rhabdomyolysis, *JAMA*, 2004;292:2622-2631.

51. The Government Accountability Office's on report on postmarket drug safety is revealingly titled "Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process."[61] The report found:

- "FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues."
- "...there is a lack of criteria for determining what safety actions to take and when to take them."
- "...FDA lacks authority to require certain studies and has resource limitations for obtaining data."
- "FDA has not clarified ODS's [Office of Drug Safety's] role in certain scientific advisory committee meetings.

52. In September of 2006 the Institute of Medicine issued a similar report, titled "The Future of Drug Safety: Promoting and Protecting the Health of the Public," which came to similar conclusions:[62]

- "The Office of Drug Safety (ODS)...has not had a formal role in drug regulation..."
- "The PDUFA mechanism that accounts for over half of CDER's funding and the reporting requirements associated with the user-fee program are excessively oriented toward supporting speed of approval and insufficiently attentive to safety."

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[61] Improvement Needed in FDA's Postmarket Decision-making and Oversight Process, Government Accountability Office, March 2006.

[62] The Future of Drug Safety: Promoting and Protecting the Health of the Public, The Institute of Medicine, National Academies Press, September 2006.

- "FDA's Adverse Event Reporting System (AERS) is outdated and inefficient...more work is needed to improve its usefulness in postmarketing surveillance.

- "...CDER's ability to test drug safety hypotheses is limited." "FDA lacks the clear, unambiguous authority needed to enforce sponsor compliance with the regulatory requirements and instead relies on the prospect of productive negotiations with industry."

3. *Labelling*:

53. A drug's label is the property of the manufacturer, not the FDA. As documented in an article published in the NEJM in 2006, a drug's label is initially drafted by the manufacturer. Modification of the manufacturer's proposed label "requires extensive and often time-consuming negotiations between the manufacturer and the FDA." After a drug is approved, the FDA only has three options in terms of requiring a drug maker to include new safety information in the drug's label: requesting the change, negotiating restrictions in the distribution of the drug, or withdrawal of the drug from the market."[63]

54. The most severe warning that the FDA places on a label is a black box. With its thick border, a black box highlights potentially serious adverse effects associated with use of the drug. In 1998, the FDA required a black box be included in the label for Propulsid because of the risk of fatal cardiac arrhythmias. A follow up study published in JAMA showed that the black box Warning (as well as a "Dear Health Care Professional" letter sent to all prescribers) had little effect, decreasing contraindicated use by only 2 percent.[64]

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[63] Ray WA, Stein CM, Reform of Drug Regulation—Beyond an Independent Drug-Safety Board, *N Eng J Med,* 2006;354:194-201.

[64] Smalley W, Shatin D, Wysowski, et al, Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action, *JAMA,* 2000;284:3036-3039.

H. Health Policy

55. Health policy decisions can be no better than the scientific evidence available to decision-makers. As shown above, it can no longer be assumed that the "scientific evidence" is complete, unbiased, or represents the best possible information. From the Journal of Health Politics, Policy and Law:

> To the extent that this evidence is biased or misleading, health services research and policy analysis are thrown off course and become unintentionally complicit in promoting inappropriate and expensive care. Regardless, health services research and policy analysis can no longer be thought of as separate from applied medical research. The game has changed. Our desire to expand access based on scientific evidence has become epistemologically naïve. The question is no longer how to provide better access, but how to determine, Access to what?[65]

56. The FDA's responsibility is to determining that new drugs are superior in efficacy to placebos, and that studies to date (though underpowered to detect meaningful safety issues) have not revealed statistically significant safety findings. The FDA's responsibility does not include guiding clinicians, insurers, formulary committees, purchasers, or policy makers about optimal therapy either in the new drug approval process or in ongoing monitoring of drug safety. My understanding is that the same holds true for Canada.

PART II – IMPACTS OF DTCA ON WOMEN AND WOMEN'S HEALTH

57. In discussing direct-to-consumer advertising and its impact on Canadians, it is important to ask whether some groups of people might be more vulnerable to potential harmful effects of DTCA than others.

58. In this regard there are several factors that indicate DTCA is likely to have unique consequences and risks for women and for women's health, when compared to the impacts of DTCA on the population as a whole.

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[65] Op. Cit. Spitz 2005

59. While our understanding of the ways in which sex and gender differences impact the effectiveness and safety of pharmaceuticals is still developing, the available evidence clearly supports continued regulation and restrictions of DTCA, and provides legislators with a strong basis of concern about the adverse effects on the population in general, and women in particular, of loosening restrictions on such advertising practices. If anything, present regulatory controls, including those in Canada, need to be strengthened.

Drug Effects in Women: Differences and Gaps in Knowledge

60. We know that because of sex differences at all levels of physiological function,[66] there may be differences (e.g., pharmacokinetics, pharmacodynamics, genetic expression; prevalence and severity of diseases; patterns of onset, course of conditions; types and responses to interventions) that impact the effect of prescription drugs. Women and men also differ in the way conditions such as depression, chronic pain, disordered eating, obesity and smoking are triggered and experienced, in their use of health care services, and in therapeutic and social interventions such as cardiac rehabilitation.

61. Wizemann and Pardue note that "it is increasingly apparent that many normal physiological functions—and, in many cases, pathological functions—are influenced either directly or indirectly by sex-based differences in biology...."[67] Increasingly, data are showing that patterns of gene expression differ, on average, between males and females, and this could lead to biological sex differences in how drugs are handled in the body. All of these differences make it difficult to extrapolate to women the results of studies of drugs carried out only in men or with a majority of men. Nevertheless these studies are routinely used as the basis for clinical decisions, and often are relied upon in DTCA, including when advertisements are directed specifically at women.

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[66] IOM report I

[67] Executive Summary of the Institute of Medicine Report, Exploring the Biological Contributions to Human Health: Does Sex Matter? *Journal of Women's Health & Gender- Based Medicine,* 2001;10:433-439.

The Unique and Adverse Effects of Many Prescription Drugs on Women's Health

62. Women and girls have specific vulnerabilities with respect to drug-induced injuries. A number of factors contribute to this vulnerability: biology, differences in patterns of health service and medication use between women and men, gender roles related to caregiving which result in women interacting more frequently with health care services, and gaps in the research evidence concerning specific effects of medicines on women. Because of both their biology and their tendency to play the central role in family health care issues, women interact with health care services more frequently than men and are prescribed more medications. This is in part due to reproductive health needs: contraception, pregnancy and childbirth, menopause, and the higher rate of chronic conditions in women, added to the fact that they live longer and experience more years of disability. For example, osteoarthritis affects about twice as many women as men. [68] All of this contributes to a higher rate of medicine use among younger (e.g., contraceptives) and older women.

63. Medications do not always have the same effect on women as on men. Certainly this is true for the prevention of heart disease. ASA for primary prevention has not been shown to be of use in women even though it is in men.[69] Although statins have been shown to be somewhat effective in high risk men in the primary prevention of heart disease, no such benefit is revealed in primary prevention studies for women.[70] And the HERS study of the effect of hormone replacement therapy on women's risk of developing recurrent heart disease, published in *JAMA* in 1998, certainly provides an example of this. Compared to women taking placebo, those randomized to take HRT developed significantly lower LDL (bad) cholesterol and significantly higher HDL-(good) cholesterol levels. Their improved lipoprotein profiles did not, however,

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[68] Rottenstein K. Monograph Series on aging-related osteoarthritis. Chronic Diseases in Canada 1997; Volume 17(3). http://www.phac-aspc.gc.ca/publicat/cdic-mcc/17-3/b_e.htmlPublic Health Agency of Canada

[69] Karin H. Humphries, et al. Outcomes of CVD in women and men – post-admission drug therapy. *Canadian Medical Association Journal Supplement*: "A comprehensive view of sex-specific issues related to cardiovascular disease", March 13, 2007, Vol 176, No 6, pp S33-S36.

[70] Abramson J, Wright JM, Are Lipid-Lowering Guidelines Evidence-Based? *Lancet,* 2007; 369;168-169.

translate into a lower risk of recurrent heart disease. (Those taking HRT did, however, experience significantly more thromboembolic and gallbladder complications.)[71] Nonetheless, clinical practice guidelines for the prevention of heart disease fail to reflect these sex-based differences (see case study on statins below).

64. There is also evidence of more vulnerability to drug-induced toxicity and some forms of carcinogenicity in women than in men. For example, a meta-analysis of the incidence of cancer in clinical trials of statins found a 33% increase in the risk of breast cancer in women taking statins compared to those in the control groups.[72] An analysis of cohort studies of 48 newly marketed drugs in Britain between 1982 and 1997 involving the experiences of more than 500,000 patients indicated that women were 60% more likely to experience a harmful drug reaction than men over the same duration of drug use.[73] This study actively followed up prescriptions of specified drugs in primary care settings by sending questionnaires to family physicians either six months or one year after an initial prescription. Only drugs for long-term use were assessed and most were new drugs. The authors hypothesized that this differential effect, which occurred in all adult age groups and across different classes of drugs, was probably dose-related and due to women's smaller average size.

65. Many drugs advertised to the public in the U.S. are also new drugs indicated for chronic use. The pre-approval clinical trials for these drugs have included limited numbers of

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[71] Hulley S, Grady D, Bush T, et al, Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women, *JAMA,* 1998;280:605-613.

[72] Krista Dale, Craig Coleman, Nickole Henyan, et al. Statins and Cancer Risk: A Meta-analysis, *JAMA. 2006,295:74-80*

[73] Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England - analysis of 48 cohort studies. *British Journal of Clinical Pharmacology.* 1998. Nov; Vol 46 No 5:505-511.

unrepresentatively healthy patients for much shorter duration than the drugs will typically be used.[74]

66. There is also evidence that when medicines have been withdrawn from the market because of serious risks discovered following market approval, women have suffered disproportionate harm. A 2001 report of the U.S. Government Accounting Office (GAO), found that of ten prescription drugs withdrawn from the U.S. market since January 1, 1997, eight of the ten posed greater health risks for women than for men. [75]

67. Four of these drugs were also prescribed more frequently to women. For example, more than 2/3 of the deaths from liver failure due to the diabetes drug Rezulin (troglitazone) occurred in women. Rezulin was advertised to the U.S. public for over two years after it had been withdrawn from the market in the UK (because of increased risk of serious liver injury). Although prescribed for patients with type 2 diabetes irrespective of sex, the GAO reports more use of Rezulin by women than men, with advertisements stressing the drug's widespread use: "more than 1, 000,000 people have begun using Rezulin to help manage diabetes."[76]

68. These drug safety withdrawals also included another DTC advertised drugs, Propulsid (cisapride, Prepulsid in Canada and New Zealand) a gastrointestinal drug which was prescribed to both women and men. Women, however, were more vulnerable to Torsades de Pointes, a potentially fatal abnormality in heart rhythm, which could be induced by the drug.[77] Safety

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[74] Ray WA, Stein Cm, Reform of Drug Regulation Beyond an Independent Drug-Safety Board, *NEJM,* 2006;354:194-201z

[75] General Accounting Office (2001). *Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women.* Washington DC GAO-01-286R

[76] Woloshin S, Schwartz LM, Tremmel J, Welch HG. Direct-to-consumer advertisements for prescription drugs: what are Americans being sold? Lancet 2001;358:1141-46

[77] General Accounting Office (2001). *Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women.* Washington DC GAO-01-286R

concerns about both Rezulin and Propulsid had been raised during the drug approval process. [78] The decision to advertise a drug to the public is a marketing decision, unrelated to the drug's safety profile. The advertisements for these drugs failed to inform the public of these safety concerns or that specific harmful effects, such as heart rhythm abnormalities and liver failure, had been noted to occur more often in women than men. In both cases there were alternative treatments with better safety profiles available.

69. The cases of Rezulin and Propulsid are particularly informative because once the demand for these drugs had been created through marketing to both patients and doctors, it was nearly impossible (short of withdrawal from the market) to modify prescribing patterns, even as evidence of serious and potentially fatal complications mounted. Despite FDA-approved label changes, including black box warnings for both drugs and multiple "Dear Doctor" letters sent directly to prescribers warning of the potential hazards of these two drugs, rational use informed by the scientific evidence was difficult to re-establish. Co-prescribing of potentially fatal classes of drugs simultaneously with Propulsid significantly decreased only after the label change and the fifth Dear Doctor letter was sent. In the case of Rezulin, after the label change and four Dear Doctor letters there was initial increase in monitoring of liver function tests (from 15% to 45%), but this was not sustained when re-examined six months later.[79]

70. I am unaware of any similar analysis of the degree of differential harm in men and women from drug safety withdrawals having been carried out in Canada. However, six of the eight listed drugs were also withdrawn from the Canadian market because of serious safety concerns, including Rezulin and Propulsid. [80]

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[78] Willman D. How a new policy led to seven deadly drugs. Los Angeles Times. December 20, 2000. Available at: http://www.latimes.com/news/nationworld/nation/la-122001fda,0,3054990.story

[79] Seligman PJ. "Dear Doctor..."---Evaluating the impact of risk communications efforts, *Pharmacoepidemiology and Drug Safety*, 2003; 12: 291–293.

[80] Lexchin J. Drug withdrawals from the Canadian market for safety reasons, 1963-2004. CMAJ 2005; 172: 765-767

71. Similarly, safety concerns were raised in the approval process for Vioxx. The FDA Medical Officer wrote in the conclusion of her analysis of the cardiovascular safety of Vioxx:

> In summary: With the available data, it is impossible to answer with complete certainty whether the risk of cardiovascular and thromboembolic events is increased in patients on rofecoxib. A larger database will be needed to answer this and other safety comparison questions.[81]

72. Nonetheless, Vioxx was approved in May of 1999 after just 3035 patient-years of clinical trial experience in patients with osteoarthritis, with the median duration of trials just 3 ½ months.[82] In 2000 (without having even started additional studies designed to determine cardiovascular risk) Merck advertised Vioxx more heavily to consumers than any other drug—and advertised more heavily even than products we typically recognize as consumer advertising-driven, like Pepsi and Budweiser beer.[83] Within the next four years—still without the additional CV outcome studies that the FDA Medical Officer had deemed necessary to determine potential risk—20 million Americans were treated with Vioxx.[84] About 70% of patients taking anti-inflammatory drugs are women.[85] And like the examples of Rezulin and Propulsid above, after the April 2002 label change, which included some of the cardiovascular risk data about Vioxx from Merck's VIGOR trial, and a Dear Doctor letter sent out to all prescribers, sales of Vioxx continued essentially unchanged.[86]

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[81] Villalba ML, FDA Medical Officer, Vioxx New Drug Application, NDA 21-042/21-052, 5/17/99. p 105

[82] Reicin AS, Shapiro D, Sperling, et al, Thrombotic Events in Patients With Osteoarthritis Treated With Rofecoxib Versus Nonselective Nonsteroidal Anti-inflammatory Drugs (Ibuprofen, Diclofenac, and Nabumetone), *Am J Cardiology,* 2002;89:204-209.

[83] National Institute for Health Care Management, Prescription Drugs and Mass Media Advertising, 2000, November 2001.

[84] McWilliams G, Jury Finds Merck Liable in Vioxx Death, *Wall Street Journal,* August 19, 2005.

[85] Ray WA, Stein M, Hall K, et al, Non-steroidal Anti-inflammatory Drugs and Risk of Serious Coronary Heart Disease: An Observational Study, *Lancet,* 2002;359:118-23.

[86] Pollack A, New Scrutiny of Drugs in Vioxx's Family, *NY Times,* October 4,2004.

Exposures during pregnancy and breastfeeding

73. As Lexchin notes, "DTCA...advocates a single treatment option for all patients regardless of their individual characteristics...and bypasses the individual nature of decision [-making by physicians]."[87] This poses problems for women and other vulnerable groups (such as children and the elderly) who are still not adequately represented in clinical trials with less information known about how they will respond to different medications. This in turn increases the potential for adverse drug reactions.

74. Consider for example that many DTC advertising campaigns target women of childbearing age. This has included some medicines for which exposure in pregnancy can lead to serious birth defects, such as the acne drug Accutane (isotretinoin). Accutane can lead to multiple malformations including of the skull and face, the heart, thymus and central nervous system, increasing the risk of major congenital malformations 25-fold.[88] Accidental exposures to medicines in pregnancy generally occur during the first trimester, when a woman is not yet aware that she is pregnant. This is also the time in pregnancy when most exposures to medicines (including Accutane) cause the most harm.

75. Because Accutane is associated with such serious birth defects and is taken by women of reproductive age, strong safeguards exist both in the U.S. and Canada to prevent accidental exposures in pregnancy. Even so, some women are exposed to the drug during early pregnancy. In the U.S. Accutane's manufacturer, Roche, began print DTCA for the drug in 1996 and added television and radio ads in 1997-8. [89] There were 900 pregnancies in women taking Accutane from 1989 to 1998 among 454,273 women enrolled in a large voluntary follow-up program.

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[87] Affidavit of Joel Lexchin sworn June 30, 2006, Respondent's Motion Record, paras. 11, 13.

[88] Lammer EJ, Chen DT, Hoar RM et al. Retinoic acid embryopathy N Engl J Med 1985; 313:837-841

[89] Chambers CD., US CDC. Accutane-exposed pregnancies – California, 1999. MMWR Weekly, January 21, 2000; 49 (2): 28-31

76. In 1999, the US Center for Disease Control carried out a study of women with Accutane-exposed pregnancies to find out if exposure might have been prevented.[90] Fourteen of twenty-three (61%) women in California recently exposed to Accutane in pregnancy agreed to be interviewed. Half (7) remembered seeing advertisements for Accutane before taking it and 4 (29%) reported being influenced to seek treatment by the ads. Some women who responded to advertising did not have severe, disfiguring treatment-resistant nodular acne. U.S. labelling warns against any other uses in women of childbearing age.

77. In Canada, notwithstanding the law prohibiting DTCA, there have been 'reminder' advertising campaigns for Accutane targeting young women. Exhibit "B-1" shows one such advertisement in a Canadian teen magazine, *Tribute*, in March 2004, four years after the publication of the US CDC study on DTCA and Accutane-exposed pregnancies. Girls as well as boys are clearly being targeted. This advertisement fails to warn of serious risks of use in pregnancy. The female model looks very young, suggesting that advertisers were targeting adolescent girls, including those under 18 years of age (legally children).

78. Although DTCA does not specifically target women who are pregnant, many advertisements target women of reproductive age, including for example antidepressant advertisements in the United States for pre-menstrual dysphoric dysfunction. Many advertisements for Paxil (paroxetine) feature women of reproductive age (see for example Exhibit "B-2").[91]

79. The point here is not that certain drugs do or do not carry a risk of foetal harm, but (as shown below) that DTC advertising has a greater impact on women, and that because of the additional biological risks associated with medication use in women of childbearing age, the risk of currently unknown and unforeseen foetal harm must be considered as potential "collateral damage" if the restrictions on DTC advertising were to become loosened in Canada.

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[90] Ibid

[91] Mintzes B. Direct to consumer advertising is medicalising normal human experience. *BMJ* 2002; 324:908-911

Targeting of women in DTCA

80. Direct-to-consumer advertisements tend to be targeted more frequently to women than to men. In U.S. print advertisements, Woloshin et al found that DTC ads appeared more often in women's magazines than men's or general readership magazines (median = 4.5 versus 2 for men's magazines and one for general readerships, p=.0001).[92] Yet another review of ads in major U.S. consumer magazines over a 10-year period by Robert Bell and colleagues found that in ads specifically targeting only one sex, women were 2.6 times as likely to be targeted in DTC advertising as men (23% vs 9%).[93] Similarly, an analysis of the quantity and placement of US television DTCA found that prescription drug ads aired most often during programs targeting women and older viewers.[94] The authors estimated that an average viewer would see more than 30 hours of DTCA each year, far more time than is spent in consultations with physicians, and that older women would be likely to view more than the average amounts of prescription drug advertisements.

81. Bell et al. also analyzed the same systematic sample of 320 magazine ads for presence or absence of key information needed for informed treatment choices.[95] They found that few provided even the most basic information needed. For example, in 9 out of 10 advertisements, no mention was made of the likelihood of treatment success or how long treatment was needed. Over 7 out of 10 failed to mention other helpful activities like exercise or diet or any other possible treatments. Little useful information was provided about the condition, with 9 out of 10 failing to correct commonly held misconceptions and three quarters failing to mention any risk

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[92] Woloshin S, Schwartz LM, Tremmel J, Welch HG. Direct-to-consumer advertisements for prescription drugs: what are Americans being sold? Lancet. 2001. Vol 358:1141-46

[93] Bell RA, Kravitz RL, Wilkes MS. Direct-to-consumer prescription drug advertising 1989-1998. A Content Analysis of Conditions, Targets, Inducements and Appeals. *Journal of Family Practice*. 2000; 49(4):329-335.

[94] Brownfield ED, Bernhardt JM, Phan JL et al. Direct-to-consumer drug advertisements on network television: an exploration of quantity, frequency and placement. Journal of Health Communications 2004: 491-497

[95] Bell RA, Wilkes MS, Kravitz RL. The educational value of consumer-targeted prescription drug print advertising. J Fam Pract 2000; 49(12): 1092-1098.

factors. It would be hard to sustain any claim that preferential targeting of women in this advertising was educational.

82. As I wrote in *Overdosed America*, much of the power of DTCA derives from substituting an emotional message in the advertising for what the viewer believes is a rational message.

> As Ernestine McCarren, General Manager of Ehrenthal & Associates, an advertising agency specializing in direct-to-consumer ads, explained in an interview for a trade magazine, "We want to identify the emotions we can tap into to get that customer to take the desired course of action. If you can't find that basic insight, you might as well forget everything else."[96]

The Use of DTCA to Promote Prescription Drug Use by Women

83. Messages in DTC advertisements targeting women do not always reflect the extent of what is known about a particular medication when used by women. For example, advertisements for statins that particularly target women (such as a recent campaign for Lipitor in Canada that used fear-laden images with women as victims – see Exhibit "B-3") ignore research that fails to demonstrate a benefit for this class of drugs in women who don't already have heart disease.[97] Additionally in the case of statins (and other classes of drugs such as anti-depressants) advertising encourages reliance upon prescription drugs when non-drug alternatives may be more appropriate. (see case studies below)

84. New Zealand (with only four million people) and the United States are the only developed countries that allow product-claim DTC advertising of prescription drugs. Drugs for conditions more common in women than in men – such as arthritis – have been the focus of some of the largest and longest running DTC ad campaigns in the U.S. and New Zealand, [98] For

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[96] Ross W, "Why Rubin-Ehrenthal Sticks Exclusively to DTC Accounts," *Medical Marketing & Media,* 1999. http://www.cpsnet.com/reprints/1999/09/McCarren.pdf access 10/14/03.

[97] Abramson J and Wright JM,. Are lipid-lowering guidelines evidence-based? *The Lancet*, 2007;369:168-169.

[98] Findlay S. Prescription Drugs and Mass Media Advertising, 2000. Washington DC: National Institute of Health Care Management, November 2001. Available at: www.nihcm.org. Accessed: December 2002

example, television ads for Pfizer's drug Celebrex (celecoxib) ran repeatedly in prime time on multiple networks in Canada in 2005-2006 (see Exhibit "B-4" and Exhibit "C-1") despite Health Canada warning letters to Canadian physicians about the possibly higher risk of cardiovascular events from use of the drug.[99] The ads targeted older women, using images that depicted a more active lifestyle courtesy of Celebrex. In addition to potentially causing harm, celecoxib has not been shown to be any more effective against arthritis symptoms than other non-steroidal anti-inflammatory drugs.[100] Nor has celecoxib been shown to provide the one advantage that has been claimed, less risk of causing serious GI complications.[101]

85. Studies indicate that, as a result of this advertising, women are more likely to request drugs from their doctors after viewing ads. For example in an FDA study of responses to fictitious advertising in a random sample of the population in 4 U.S. cities, both women and the elderly were more likely to say they would ask their doctor for a prescription in response to advertising.[102] There is also evidence that, compared to men, women are more likely to use advertising as an information source on prescription medicines. For example, a New Zealand survey of the general public found that 29% of women reported having used a magazine or newspaper advertisement as an information source about medicines and other treatment while

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[99] Health Canada safety advisory available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2004/2004_69_e.html

[100] Witter J, Medical Officer Review Celebrex, Review Date September 20, 2000. pp50-53.

[101] Goldkind L, FDA Medical Officer's Gastroenterology Advisory Committee Briefing Document, Febraury 7, 2001. http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_05_gi.doc accessed 9/26/01.

[102] Morris LA, Brinberg D, Klimberg R, Millstein L, Rivera C. Consumer attitudes about advertisements for medicinal drugs. Soc Sci Med 1986;22(6):629-38.

only 15% of men reported using a magazine or newspaper advertisement as an information source. [103]

CASE STUDIES

86. The following case studies illustrate some of the key themes identified above:

1. Advertising directed at women based on assumptions from studies in men.

Statins

87. There has never been a single clinical trial showing that statin therapy is beneficial for women who don't already have heart disease or diabetes. Data was pooled by UBC's James Wright of all eight randomized control trials that compared statins with placebo in primary prevention populations at increased risk. In 10,990 women studied, statins did not reduce total coronary heart disease events in this population.[104] Assumptions about the benefit of statins for women who do not have pre-existing heart disease or diabetes are repeatedly based on data from extrapolated from primary prevention benefit documented in men and secondary prevention studies (involving only people who already have heart disease).

88. In February 2007, the American Heart Association issued "Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update".[105] The Guidelines start with the oft-repeated but misleading statement that "cardiovascular disease is the largest single cause of death among women, accounting for one third of all deaths." In fact, before the age of 75

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[103] Toop et al. 2003 Op Cit, ref 28. Colmar Brunton consumer survey, described in the appendix to the report. P.77.

[104] Abramson and Wright, 2007, *op cit*

[105] Mosca L, Banka CL, Benjamin EJ, et al, Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women: 2007 Update, *Circulation* published online Feb 19, 2007. DOI: 10.1161/CIRCULATIONAHA.107.181546

cancer is responsible for 78% more deaths than heart disease. Not only is there no evidence from RCTs that statins are beneficial for primary prevention in women, but neither is there evidence that they are beneficial for primary prevention over the age of 65 for men or women. [106]

89. The Guidelines specifically and appropriately underscore the lesson learned from the Women's Health Initiative study: observational studies (in that case about HRT) can lead to misleading conclusions and calls for reliance on clinical trial data:

> Demand for clinical trial evidence increased in the wake of the Women's Health Initiative's discordant findings with observational studies of hormone therapy. Some commonly used preventive interventions lacked clinical trial data for women, and it was unclear whether results of studies conducted in men could be generalized to women. Since the 2003 literature review, numerous clinical trials that have bearing on CVD prevention in women have been completed (see Appendix).

90. The section titled "Research Needs and Future Directions" presents several "gaps in knowledge related to the prevention of CVD that must be addressed to optimize the cardiovascular health of women": testing of the impact of the guidelines; testing effective ways to implement the guidelines; studying the role of communication of risk, the role of genetics; and the effect of female sex on the prognostic value of new biomarkers. Notably absent from this list is the still outstanding need to determine whether statins provide any benefit to women without heart disease.

91. Notwithstanding the lack of evidence from clinical trials, the guidelines recommend statin therapy for primary prevention in three risk categories of women:

- Utilize LDL-C lowering therapy if LDL-C is ≥130 mg/dL with lifestyle therapy and there are multiple risk factors and 10-year absolute risk is < 10% to 20% (Class I, Level B)

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[106] Abramson, Overdosed America, pp. 139-142

- Utilize LDL-C lowering therapy if LDL-C is ≥mg/dL with lifestyle therapy and multiple risk factors and 10-year absolute risk is < 10% (Class I, Level B)

- Utilize LDL-C lowering therapy if LDL-C is ≥190 mg/dL regardless of the presence or absence of other risk facts or CVD on lifestyle therapy (Class I, Level B)

Note that Class I means: "Intervention is useful and effective." Level of Evidence B means: "Limited evidence from single randomized trial or other nonrandomized studies"

92. In the Appendix to the Guidelines — Bibliography by Topic: *Hyperlipidemia* — nine studies are cited to support the above recommendations: eight of the studies involve only people who already have coronary artery disease and the ninth includes only people with type 2 diabetes.

93. The recommendations for statin therapy for primary prevention in women of these "Evidence-Based Guidelines", which are endorsed by the American Heart Association, are lacking exactly the kind of evidence that the guidelines themselves deem necessary: clinical trials – a gap that is not even acknowledged.

94. It is not likely that practicing physicians reading these guidelines will understand that there is no evidence from RCTs to support the use of statins as a primary prevention treatment for women.

95. In their recent analysis of the literature on statin use in women, Canadian researchers Rosenberg and Allard found "a pattern of overestimation of benefit and underestimation of harm".[107] Furthermore, a study that followed 7300 women for 31 years shows that elevated

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[107] Rosenberg, Harriet and Allard, Danielle. Evidence for Caution: Women and Statin Use. Women and Health Protection. March 2007. p. 26.

cholesterol in women has no effect on overall mortality rate, and does not even significantly increase cardiovascular disease or coronary heart disease mortality rates.[108]

96. The prominent role that women -- usually healthy appearing women for whom no mention is made of pre-existing heart disease or diabetes -- play in advertisements for statins is clearly intended to make viewers, listeners, and readers believe otherwise. The prominence of women in statin advertisements aimed at consumers shows clearly how DTCA is used to expand markets for expensive drugs by presenting images that are not necessarily supported by scientific evidence. The heavy DTCA marketing of statins also shows clearly how these ads mislead consumers into believing that heart disease can be prevented by taking a pill when the evidence shows clearly that the most effective ways to prevent heart disease are routine exercise, a healthy Mediterranean style diet, not smoking, drinking in moderation, and maintaining a healthy body weight.[109], [110]

97. Despite what we know about the limited usefulness of statins for women, they are targeted equally in advertisements for this class of drugs. In Canada, Pfizer (the manufacturers of the #1 top-selling statin drug,[111] Lipitor) ran a lengthy campaign over several months that used the tagged toe of a corpse to promote cholesterol testing among women in their 50s without heart disease. (See Exhibit "B-5"[112]). This full-page ad ran in major newspapers and women's magazines across Canada and carried the logo of the Canadian Lipid Nurses Network, an

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[108] Daviglus M, Stamler J, Pirzada A, et al, Favorable Cardiovascular Risk Profile in Young Women and Long-Term Risk of Cardiovascular and All-Cause Mortality, *JAMA,* 2004;292:1588-1592.

[109] Stampfer MJ, Hu FB, Manson JE, et al. Primary Prevention of Coronary Heart Disease in Women through Diet and Lifestyle. *New England Journal of Medicine.* 2000;343:16-22.

[110] Abramson, Overdosed America, pp. 220-225.

[111] IMS Health Canada. Drug treatment insights: cholesterol reducers among the world's top prescribed medication. 2006.

[112] Pfizer and Canadian Lipid Nurses' Network. Which would you rather have, a cholesterol test or a final exam? Chatelaine 2001;74(9):745.

organization funded by Pfizer Canada to "educate Canadians about the role of cholesterol as an important risk factor in the development of heart disease and the risk of stroke".[113]

98. DTCA of pharmaceutical treatment options has been shown to reduce the likelihood of patients engaging in lifestyle management options. In a paper in 2005, Iizuka et al showed that DTCA related to four chronic conditions -- diabetes, high cholesterol, over weight, and hypertension -- reduced the likelihood of engaging in moderate exercise.[114] In this case study of cardiovascular risk, the overestimation of benefit misleadingly directs women to a management option that is not helpful. This will lead to unnecessary expense and unnecessary exposure to the still unknown risk of adverse effects associated with long-term exposure to statins. But even more important is the enormous lost opportunity-cost of diverting the limited time that doctors and patients have together, from what should be a conversation about the most effective ways to minimize the risk of heart disease that reflects the best scientific evidence, to one about the merits of a particular product based on what the patient gathers from being exposed to evidence that is most commercially advantageous to the product manufacturer.

99. A study of the content of U.S. television advertising is consistent with the effects on behaviour found by Iizuka et al. Dominick Frosch and colleagues examined a sample of pharmaceutical advertisements during peak viewing times in June and July, 2004. They found that none of the advertisements described healthy activities or other lifestyle changes as an alternative to medicines. The authors comment that, "Several ads for cholesterol-lowering drugs appeared to suggest that nonpharmacological approaches were almost futile."[115] One advertisement for Lipitor featured a healthy-looking athletic woman who is presented as running

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[113] "International survey finds Canadians uncertain about healthy cholesterol targets" Press release, Pfizer September 4, 2001 http://www.pfizer.ca/english/newsroom/press%20releases /default.asp?s=1&year=2001&releaseID=62

[114] Iizuka T, Zhe Jin G. Drug advertising and health habits. Cambridge, MA.: National Bureau of Economic Research 2005. http://www.nber.org/papers/w11770. Accessed 26 April 2006.

[115] Frosch DL, Krueger PM, Hornik RC, et al, Creating Demand for Prescription Drugs: A Content Analysis of Television Directo-to-Consumer Advertising, *Annals of Family Medicine,* 2007:5:6-13.

3 miles a day, eating low-calorie lunches, and is a basketball coach. The message is that this healthy lifestyle is not adequate, and her high cholesterol must be treated with drugs. The important point is that these advertisements have the singular purpose of focusing the viewers' attention on cholesterol levels—which may or may not respond to lifestyle interventions. Like a good magician the ads distract viewers' attention from the primary concern: reducing the risk of developing heart disease and improving the overall chances of staying healthy. Cholesterol level is a surrogate endpoint, which may or may not correlate with better health, but the ads masterfully create the impression that the ultimate goal is lowering cholesterol rather than improving health.

2. Advertising that encourages the favouring of drugs for conditions where non-drug alternatives may be more appropriate[116] and drug treatments that are associated with serious risks

SSRI Anti-Depressants

100. The increase in diagnosis of depression and treatment with prescription drugs – for both men and women - has been well documented in the medical and social scientific literature. The use of psychotropic medication into the 21st century has become so widespread, as one author notes, that these drugs "have shaped our language, culture and assumptions about sickness and health".[117] In a relatively short period, they have become "society's main response to distress..."[118]

101. Women are more likely to be diagnosed with depression and prescribed anti-depressants than men. Using data from the National Ambulatory Medical Care Survey in the U.S., Simoni-

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[116] Ibid (Iizuka et al)

[117] Currie, Janet. *The marketization of depression: The prescribing of SSRI anti-depressants to women.* Women and Health Protection. May, 2005 http://www.whp-apsf.ca/pdf/SSRIs.pdf

[118] Moncrieff, Joanna and Kirsch, Irving. Efficacy of anti-depressants in adults. *British Medical Journal* 2005, Vol 331: 155-157.

Wastali found that the probability of receiving any psychotropic drug (including anti-depressants and anxiolytics) was 55% greater in office visits by women than those by men.[119]

102. The significant increase in prescriptions for anti-depressants is happening despite evidence of their limited effectiveness.[120] Analysis of all pivotal studies of new generation anti-depressants submitted to the FDA between 1987 and 1997 obtained on a *Freedom of Information Act* request revealed that the new antidepressants provided less than 10 percent greater relief of the symptoms of major depression than placebo (40.7% symptom reduction with the new antidepressants vs. 30.9% with placebo).[121]

103. It is worth contrasting this body of scientific evidence on the effects of antidepressants with the messages in DTCA. For example, the attached advertisement for sertraline (Zoloft) purports to present the story of a 27 year-old woman, Jen (Exhibit "B-6"). The impression given is that the antidepressant works 100% of the time, with the fictitious 'Jen' transformed from being blue to feeling happy again.

104. For the purposes of this discussion, it is noteworthy that studies of DTC advertisements of antidepressants have shown that these ads predominantly target women.[122]

Diane-35 (acne medication used for birth control)

105. The drug Diane-35 (cyproterone and estradiol) is approved in Canada for the treatment of severe acne in women who had signs of hormone imbalance (androgenization) and who had not

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[119] Simoni-Wastili, L. Gender and psychotropic drug use. *Medical Care.* Vol. 36, No 1 January 1998: 88-94

[120] Moncrieff & Kirsch, *op cit*

[121] Khan A, Warner HA, Brown WA, Symptom Reduction and Suicide Risk in Patients Treated with Placebo in Antidepressant Clinical Trials: An Analysis of the Food and Drug Administration Database, *Archives of General Psychiatry,* 2000;57:311-317.

[122] Multiple citations in Grow JM, Park, JS and Han, X. "Your Life is Waiting!": Symbolic Meanings in Direct-to-Consumer Antidepressant Advertising . *Journal of Communication Inquiry.* Vol 30 No 2, April 2006: 163-188

responded to oral antibiotics or other acne treatments.[123] It was marketed for birth control and as an acne treatment in Europe, Latin America, Australia and Asia. In Canada, it was approved later than in Europe (in 1998), after safety concerns had already led to a restriction in use in Europe.[124] It has never been approved for contraceptive use, for mild or moderate acne, or as a first-line acne treatment in Canada. It has never been approved for any use in the U.S.

106. Diane-35 is associated with a four-fold higher risk of thromboembolism (potentially fatal blood clots) than commonly used birth control pills that contain the progestin levonorgestrel.[125] Health Canada has repeatedly sent out warnings about the safety of Diane-35.[126] Nevertheless throughout this period a number of print and television advertisements featuring Diane-35 in a manner that would encourage it to be used for non-approved purposes appeared in Canadian media (see for example the attached advertisement for Diane-35 in *Healthy Woman* magazine and the television advertisement Diane-35, which are included as Exhibits "B-7" and "C-2" to this affidavit respectively).

107. These advertisements feature young girls who look 15 or 16 years of age, with unblemished skin and glowing smiles. The images in these advertisements are strikingly inconsistent with the approved product use: a woman who has severe acne that has failed to

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[123] Mintzes B, Morgan S, Bassett KL. Medicine by media: did a critical documentary affect the prescribing of cyproterone-estradiol (Diane-35)? CMAJ 2005; 173:1313-1314

[124] Ibid.

[125] Vasilakis-Scaramozza C, Jick H. Risk of venous thromboembolism with cyproterone or levonorgestrel contraceptives. Lancet 2001; 358: 1427-1429; Wooltorton E. Diane-35 (cyproterone acentate): safety concerns. CMAJ 2003; 168: 455-6.

[126] Health Canada. HPFB. Therapeutics Products Directorate. Important Safety concerns on the use of Diane-35. Ottawa: December 19, 2002; Stril J-L, Berlex Canada and Health Canada. Important Drug safety Information about Diane-35 and the riskof venous thromboembolism. 'Dear Health Professional' letter. Pointe-Claire, Quebec: April 10, 2003. Health Canada. Advisory. Health Canada advises consumers of new warning for Diane-35. May 12, 2005. [126]://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_39_e.html

respond to previous acne treatments – the only use approved in Canada – is highly unlikely to look like the models in these advertisements.

108. A critical television documentary on Diane-35, which aired in January 2003, included interviews with young women and family physicians who believed (incorrectly) Diane-35 was a birth control pill.[127] An analysis of newly initiated prescriptions in British Columbia from 1998 to 2003, combined with information on previous medical consultations, diagnosis, and prescriptions, found that 46% of new users had no evidence of previous acne diagnosis or treatment or any consultations with a dermatologist.[128] Both of these indicate how advertising campaigns can lead to misleading understandings by consumers and physicians, as well as to potentially harmful effects.

109. Eight deaths have been reported in Canada in which Diane-35 was the suspected cause.[129] The average age of these women was 23; two were 18 years of age. In total, there have been 157 suspected adverse reactions to Diane-35 reported to Health Canada as of April, 2007.[130] There is good evidence of under-reporting of adverse reactions to this drug, as the rate of reports jumped ten-fold, from an average of 0.4 per month to an average of 4.6 per month, following the critical TV documentary on Diane-35 aired by CBC noted above.[131]

110. Acne is not a life-threatening condition and there are safer alternatives for birth control than Diane-35. The case of Diane-35 not only highlights avoidable harm to young women in

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[127] CBC Disclosures. Two-for-one. January 14, 2003. Transcript available at www.cbc.ca/disclosure/archives/030114_diane/main.html (accessed Nov 24, 2004)

[128] Mintzes B et al, 2005 op.cit.

[129] Health Canada. Adverse Drug Reaction Database. Diane-35. Accessed April 26, 2007. Available at: http://cpe0013211b4c6d-cm0014e88ee7a4.cpe.net.cable.rogers.com/CADRMP/LoadResultsAction.do?recordNumber=1

[130] Ibid

[131] Mintzes B. Drug regulatory failure in Canada. The case of Diane-35. Women and Health Protection. October 2004. Available at: www.whp-apsf.ca/pdf/diane35.pdf

Canada, but also raises serious questions about the capacity of the regulatory structures and processes in Canada to prevent serious and unnecessary harm as a consequence of exposure to advertising. The case also serves to illustrate that even in the context of the current limitations on DTCA in Canada, drug companies and advertisers still find ways to promote the sale of drugs for non-approved and often harmful uses.

Hormone replacement therapy to women

111. 1966 marked a turning point in the marketing of hormone replacement therapy, brought about by the publication of Dr. Robert Wilson's best selling book, *Feminine Forever.*[132] This was the first intensive promotion of hormone replacement therapy to the public. The book, produced for a mass audience, captured the promotion of menopause as a "galloping catastrophe" which must be eliminated, views which had been aired in medical journals during the previous three years. But unlike the material aimed at medical professionals, Wilson's book was targeted directly to those who were the most vulnerable to messages about lost youth, sexuality and desirability at the onset of menopause. Wilson also suggested the cure for what he defined as "estrogen deficiency" (analogous to insulin deficiency as the cause of diabetes): estrogen replacement therapy.

112. More than 40 years after the book was published it was revealed in the New York Times that "Wyeth-Ayerst had paid all the expenses of writing 'Feminine Forever' and financed [Wilson's] organization, the Wilson Research Foundation". Furthermore, "the company had also paid [him] to lecture to women's groups on the book".[133] By the time this news reached the public, however, Wyeth's HRT products had been among the top 50 selling drugs in the US for

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[132] Robert A. Wilson, Feminine Forever (New York: Evans, 1966)

[133] Gina Kolata, Hormone Replacement Study A Shock to the Medical System, New York Times, July 10, 2002

almost four decades.[134] By the end of the 2001, almost half (42%) of all post-menopausal women in the United States were being treated with long-term hormone replacement therapy.[135]

113. As is typically the case, promotional activities for HRT were multifaceted. For example, an analysis of the underlying messages presented in advertising for hormone replacement therapy in Canadian medical journals during the 1980's, 1990's and 2000 found that these advertisements used and reinforced stereotypical views of women. The authors point out that this results in harm, "The messages of drugs ads imply certain things about women that are not in women's best interests or in the interests of the doctor-patient relationship." [136] The most recent advertisements that were examined in this study were from 1997 and 2000. These ads highlighted long-term benefits of hormone therapy. Although they preceded the results of the Women's Health Initiative trial, which showed that long-term use of hormone therapy was more likely to result in harm than benefit,[137] it is important to note that these claims of overall benefit had not been substantiated by evidence from randomized clinical trials. And it is also important to note that these ads were pre-screened in Canadian medical media. The example is relevant to the risks of extending DTCA in Canada because it shows the limited extent to which pharmaceutical regulation in Canada is able to protect women against harmful stereotyping and unsubstantiated health claims.

114. These and other efforts to promote the use of HRT resulted in it being among the most heavily promoted medications prior to the report of the Women's Health Initiative Estrogen Plus

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[134] Jocalyn Clark, A hot flush for Big Pharma, BMJ. 2003 August 16; 327(7411): 400

[135] Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA. 2004;291:47–53

[136] Peppin P, Carty E. Semiotics, stereotypes, and women's health: signifying inequality in drug advertising. Canadian Journal of Women and the Law 2001; 13 (2).

[137] Writing Group for the Women's Health Initiative Investigators, Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women, *JAMA*, 2002;288:321-333.

Progestin Trial in July 2002.[138] Indeed, according to the National Women's Health Network "The widespread popularity of hormone replacement therapy in the United States is a triumph of marketing over science and advertising over common sense"[139]

115. Between 1992 and 1999, Wyeth-Ayerst's promotion of Premarin made it the leading drug in the number of prescriptions dispensed out of the top 200 drugs marketed in the United States. When Premarin, a conjugated estrogen prescribed for women in the menopausal and perimenopausal years, was promoted to physicians during the 1980s, the focus was primarily on the symptomatology of menopause. But in the late nineties, the focus changed, in concert with the increase in direct-to-consumer advertising, to the prevention of serious diseases such as heart disease, osteoporosis, and Alzheimer's.[140]

116. Unfortunately, while advertising directly to consumers helped boost the bottom line of manufacturers, it did very little to increase knowledge among the public about the benefits and risks associated with hormone replacement therapy. In the first 18 months after the FDA loosened the restrictions on television advertising of prescription drugs in the US, ads for 17 of the 33 drugs advertised were found to have violated the regulations, most commonly by downplaying risks. Some ads also exaggerated benefits and implied that the products could be used to treat a wider range of conditions than the government approved them for.[141]

117. The information that women needed to make an informed decision about hormone replacement therapy was not obtained in direct-to-consumer advertising. In fact, the opposite was

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[138] Majumdar, S.R., E.A. Almasi, R.S. Stafford, Promotion and Prescribing of Hormone Therapy After Report of Harm by the Women's Health Initiative, JAMA, October 27, 2004—Vol 292, No. 16.

[139] Response to FDA Request for Comments, September 13, 2002, National Women's Health Network. The NWHN was commenting on the FDA's policies, regulations, guidances, practices and compliance with US First Amendment guarantees of freedom of speech.

[140] Peppin, Patricia and Elaine Carty, Semiotics, Stereotypes, and Women's Health: Signifying Inequality in Drug Advertising, Canadian Journal of Women and the Law, Volume 13, Number 2, 2001.

[141] Mintzes, Barbara and Baraldi, Rosanna, Direct-to-Consumer Prescription Drug Advertising: When Public Health is No Longer a Priority (Montreal: DES Action Canada, 2001).

true. The advertisement attached as Exhibit B-8, which ran in the magazine *Parade*, which was included as a Sunday supplement on March 19, 2000, uses a celebrity endorsement to promote HRT use. The image of a youthful-looking Lauren Hutton also helped to misleadingly suggest that estrogen prevents age-related physical changes. The ad refers to ongoing research to make a number of claims supporting effects that had never been established and for which the drug had not been approved. The pre-Women's Health Initiative claims that HRT prevented heart disease and dementia now highlight the excesses of marketing to consumers, since the scientific evidence from the Womens Health Initiative showed exactly the opposite.

118. The 2002 release of the WHI study triggered an immediate drop in the number of prescriptions for hormone replacement therapy around the world. Before the study was published, 22.4 million prescriptions for hormone therapy were written and $71 million was spent on promotion,[142] approximately 15% of which was targeted directly to consumers.[143] Nine months after the WHI published its evidence of increased risk of breast and ovarian cancer the number of prescriptions for HRT fell by 32%, while direct to consumer advertising fell by 100%, followed by a decline in promotional samples of 36%.[144]

119. In 2003 the results of the "Million Women Study," were published in *The Lancet*.[145] Literally one million women in the UK participated in this study, after being enrolled when they received their routine mammograms. The results showed that women who were currently taking hormones had a 66 percent higher chance of getting breast cancer (30 percent for those taking only estrogen, and 100 percent for those women taking both estrogen and progesterone) than the women who were not taking hormones. The women taking hormones were also significantly

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[142] Majumdar, et al, Op.Cit.

[143] Peppin, Carty, Opcit. This estimate is based on the average portion of overall drug promotion targeted directly to consumers in 2000 in the United States.

[144] Majumdar, et.al., op.cit

[145] Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *The Lancet*. 2003;362:419-27.

more likely to die of breast cancer than the women not taking hormones. The researchers calculated that there had been about 20,000 extra cases of breast cancer caused by HRT in the UK over the previous ten years.

120. Based on the difference in population size alone, even at the same rate of hormone use, there would have been an extra 94,000 cases of breast cancer in the US in the previous 10 years as a result of taking HRT. In the United States, use of HRT had been about four times greater than in the UK in the early 1990s and therefore the number of breast cancers caused by HRT would be approximately 400,000.

121. The Million Women Study also showed that for women with an intact uterus, adding progesterone to estrogen does indeed reduce the risk of uterine cancer: taking estrogen with no progesterone causes an extra 10 uterine cancers and 5 extra breast cancers per 1000 women over 10 years. Adding progesterone causes an extra 19 breast cancers per 1000 women over the same 10 years. In other words, the problem with uterine cancer was solved by adding a drug that *increased* a woman's overall risk of getting cancer by 27 percent.

122. Corroborating the findings from the Million Women Study, the rate of breast cancer in the United States has declined by 8.6% from 2001 to 2004.[146] This decline in the incidence of breast cancer coincides with a two-thirds decline in the number of prescriptions being written for HRT after the findings of the Women's Health Initiative study became known in 2002. Prior to 2002, while HRT was being advertised so aggressively to women promising many unproven benefits, the real effect of the advertising was to greatly increase the number of breast cancers developing in American women.

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[146] Ravdin PM, Cronin KA, Howlader N, et al, The Decrease in Breast-Cancer Incidence in 2003 in the United States. *NEJM*, 2007;356:1670-1674.

CONCLUSIONS

123. DTCA must be viewed in context, and when this is done, two important points emerge. The first arises from the increasing control that drug companies have gained over primary research, publishing and other modalities through which information concerning the efficacy and risks associated with prescription drug use is disseminated. Drug companies now exert an unprecedented influence over the drug approvals process as well. This lack of independent research, review, analysis and communication has undermined the reliability of information about the benefits and risks of prescription drug use, including as this is conveyed to medical professionals (even from the sources they have been taught to trust) and policy makers. Medical professionals and policy makers must read articles published in peer reviewed journals and even primary research reports with much more vigilance and attention to what is said, or may not be said, than ever before. But even increased vigilance does not mitigate the entirety of this problem—it is not uncommon for the correct information to simply not be available to even the most disciplined readers of the medical literature. The distortions of medical "knowledge" by this commercial bias are seriously compounded for lay persons confronted with DTCA.

124. The second is that DTCA is but one aspect of the multi-faceted promotional activities that drug companies routinely deploy to promote the sales of their products. These have presented regulatory officials with unprecedented challenges, which increasingly are leading to the approval and use (for approved purposes or off-label use) of drugs that pose considerable risks. As a result, hopeful patients, who are ill-apprised of these risks, may take new drugs that are more likely to cause harm or do not have as advantageous a risk/benefit ratio as already established drugs.

125. The impact of DTCA on other promotional activities by drug manufacturers has particular relevance for women and women's health. This arises from the various factors that have been described above and that are illustrated in the case studies of several popular medications that, as I have related, pose greater risks than benefits for women to whom they are actively marketed. Because of the particular risks DTCA presents for women, any consideration

of the putative benefits associated with such promotional activity must be assessed against the risks posed for them specifically and beyond those for the population in general. As I have related, these risks are considerable and often have grave consequences. In light of the seriousness of these risks there is ample justification and a sound and empirical basis for maintaining, and in fact strengthening regulatory control of DTCA. This is certainly true for the United States where the regulatory system is failing to provide adequate protection for consumers from the adverse effects of DTCA. And this is true for Canada as well, where the same problems have emerged notwithstanding the more limited scope of DTCA.

AFFIRMED BEFORE ME at the City of Ipswich, in the State of Massachusetts, on May 7, 2007.

STEVEN ROBERT McCLENAGHAN
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 8, 2011

DR. JOHN ABRAMSON

STEVEN ROBERT McCLENAGHAN
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 8, 2011

This is Exhibit.....A.....referred to in the affidavit of.....Dr. John Abramson.....
sworn before me this.....07.....
day of.....May.....20.....07.....
A COMMISSIONER, ETC.

EXHIBIT A

John Abramson, MD

Professional Address: 39 Spring Street, Ipswich, MA 01938

Email: john_abramson@hms.harvard.edu

Phone: 978-312-1225

Place of Birth: Cambridge, MA

Education:

1970	BA cum laude	Harvard College	Social Relations
1971-2		Harvard College	Premedical courses
1974	BMS	Dartmouth Medical School	Medicine
1976	MD	Brown Medical School	Medicine

Postdoctoral Training:

1982	MS	Case Western Reserve University	Family Medicine
1976-77	Internship	Memorial Hospital, Chapel Hill, NC	Family medicine
1979-81	Residency	University Hospitals of Cleveland, OH (Case Western Reserve University)	Family practice
1980-82	Fellow	Case Western Reserve University	Robert Wood Johnson Fellow in Family Medicine

Licensure and Certification:

1982	Massachusetts Board of Registration in Medicine. License No. 49182
2001	Diplomate, American Board of Family Practice 1982, recertified 1989, 1995, 2001

Academic Appointments:

1992-3	Senior Research Associate, Institute for Health Policy, The Heller School, Brandeis University
1997-School	Clinical Instructor, Dept. of Ambulatory Care and Prevention, Harvard Medical

Hospital or Affiliated Institution Appointments:

1982-2002	Medical Staff	Beverly Hospital
1994-2002	Medical Staff	Lahey Clinic

Other Professional Positions and Major Visiting Appointments:

1977-9	National Health Service Corps, US Public Health Service
1982-2002	Family physician, Hamilton-Wenham Family Practice, Hamilton, MA
1986-1993	Associate Medical Director, Pru-Care of MA
1994-2001	Chair, Department of Family Practice, Lahey Clinic, Burlington MA
2005-present	Executive Director of Health Management, Acordia (a Wells Fargo Company)

Hospital and Health Care Organization Service Responsibilities:

1989-1991	Member, Board of Trustees, Beverly Hospital

Major Committee Assignments:

1993-5	Chair, Graduate medical Education Committee (Family Practice Residency), Beverly Hospital

Professional Societies:

1982-2002	Massachusetts Medical Society
1982	American Academy of Family Practice

Awards and Honors:

1996, 1999	Community Newspapers "Readers' Choice Award for Best Doctor", Beverly, Hamilton, Wenham
1999	Center for the Study of Services "Guide to Top Doctors"
2000	Castle Connolly/Town and Country's Guide to Primary care Physicians
2001	Castle Connolly/AOL-Digital City "Guide to Top Doctors"
2002	Selected to be included in Lady's Home Journal: The Best Family Doctors in America (had left practice to write book so name did not appear in magazine)
2003	Profiled in Harvard Magazine article: "Doctored Research?" Nov-Dec issue

Part II:
Research. Teaching, and Clinical Contributions

A. Primary Care Clerkship and mentorship program: Harvard Medical School, preceptor of third-fourth year student for the next eight years. Teaching activities have also included the elective course and independent study in "Healing and Spirituality" as listed below.

D. Report of Teaching
1. Local Contributions

1992-1994	Harvard Medical School Two years Primary Care Mentorship Program Mentor One first-year medical student per year
1994-2001	Harvard Medical School Eight years (One student per year) Primary Care Clerkship Preceptor
1999-2001	Harvard Medical School Three years (average 12 students per year) Healing and Spirituality in Medicine Elective Faculty 1999, Course Co-director 2000 and 2001
2002	Harvard Medical School Independent Study Healing and Spirituality
2002-2007	Harvard Medical School Ongoing Primary Care Clerkship Tutor
2003	Harvard Medical School Independent Study Healing and Spirituality

2. Presentations:

1981	A prepaid primary care network for private and AFDC patients: an alliance between the private and public sectors. National Governor's Association Conference on Primary Care Networks, New Orleans, LA.
1982	Participation of a residency based family practice center in an innovative case management program. Society of Teachers of Family Medicine, Chicago, IL.
1983	The economic impact ofa primary care network on primary care physicians and Medicaid costs. Robert Wood Johnson Foundation, Princeton, NJ.
1984	Primary care of de-institutionalized retarded adults in the community. HCFA Meeting of Federal Surveyors of Intermediate Care Facilities, Portland, ME.
1991	The role of physicians in the Michigan Comprehensive Community Health Models Project. Pew Health Policy Annual Meeting, Cambridge, MA
1999	The role of the physician/patient relationship in the healing process. Topics in Internal Medicine (Lahey Clinic), Portsmouth, NH
2002-5	Healing our Critically Ill Health Care System. Clinical Training in Mind/Body Medicine. Mind/Body Medical Institute/Harvard Medical School Continuing Education, Boston, MA
2004	The Quality of Our Medical Knowledge: Vioxx and Statins. Heller School for Social Policy NCEP Recommendations: Preventing Heart Disease or Pushing Drugs?. Encino-Tarzan Regional Medical Center, CA. Grand Rounds, Beverly Hospital Beverly MA: NCEP Recommendations: Preventing Heart Disease or Pushing Drugs?
2005	Williams College; Lessons from Vioxx: Misinforming Doctors, Harming Patients and Making money, 1/11/05 New York City Department of Public Health, Chronic Disease Grand Rounds, 2/4/05 Bellevue Hospital Medical Seminar 2/9/05 Denver Forum, Denver CO 2/10/05 Woman's National Democratic Club, Washington DC, 3/3/05 Congressional Task Force on Prescription Drugs, Washington DC, 3/3/05 Mind Body Medical Institute Harvard Medical School 3/23/05 San Diego City Club 4/8./05 Alternative Therapy Conference, San Francisco, Keynote Address: "Overdosed America." 4/9/05 University of Michigan (Undergraduate course in health policy) 4/05/05 Health Care Benefits Forum, Chicago Hyatt Regency, Keynote Address: 4/7/05 City Club of San Diego, 4/08/05 Alternative Health Conference, San Francisco CA 4/9/05 Harvard Medical School, Cabot Lecture Series, 4/25/05 Drug Therapy Conference, British Columbia 4/16/05 Lutheran Medical Center, Brooklynn NY, 4/27/05 Cooley Dickinson Hospital, Northampton MA 4/29/05 Harvard School of Public Health, 5/02/05 Southern Vermont Area Health Education Center, 5/07/05 Chilten Club of Boston, 05/26/05 Hiram B. Curry Memorial Lecture, University of S. Carolina Dept Family Practice, 6/6/05 Harvard Medical School, Mind/Body Medical Institute Continuing Medical Education 6/15/05 Vermont Citizens Campaign for Health 6/16/05 Medical Foundation of Boston, 6/21/05 Harvard Club of Boston, 6/22/05 Hamilton Wenham Public Library 6/23/05 World Pension Forum, Chatham MA, 7/12/05

Boulderfest, Boulder CO, 7/14/05
Center for Popular Economic, Amherst MA, 8/1/05
Public Policy Virginia, Roanoke VA, 9/17/05
Fletcher Allen Hospital, Burlington Vermont 9/26/05
University of Vermont Medical School 9/26/05
Central Vermont Hospital 9/27/05
Vermont Medical Society 9/27/05
Cayuga Medical Center of Ithica, 9/30/05
Michigan State Medical Society Bioethics Conference, 10/08/05
Harvard Medical School, Mind/Body Medical Institute Continuing Education Course 10/17/05
U Mass Med School, Community Medicine 10/19/05
Massachusetts Medical Society/Medical students 10/19/05
Rotary Club, Charleston, WV, 10/21/05
National Legislative Association on Prescription Drug Prices, Charleston, WV 10/21/05
League of Women Voters, Hamilton, MA, 10/30/05
Sharp Medical Center, San Diego, CA 11/04/05
Pacific College Symposium, San Diego CA 11/05/05
Allegheny General Hospital, Pittsburgh, PA 12/7/05

2006

LA Country Employee Pension Association 1/26/06
West Virginia House and Senate 2/1/06
George Washington Medical School panel about Drug reps on campus 2/9/06
HealthFirst Conference 2/22/06
Cambridge Health Alliance Family Medicine Grand Rounds 2/24/06
Harvard Medical School Pharmacology Patient Safety Session "The Vioxx example" 2/28/06
Nieman Journalism Fellowship 3/1/06
Sudbury League of Women Voters 3/5/06
Bentley College, Business Ethics Lecture 3/7/07
Northwest Pharmacy Benefits Managers-Medical Directors Conference, Seattle WA 3/10/06
Harvard Medical School Continuing Medical Education, Mind Body Medicine 3/13/06
Association of Health Care Journalists, Houston TX, 3/17/06
North Shore Seminars, Beverly MA 3/19/06
New England Biolabs, Ipswich MA 3/23/06
Florida State University Medical Grand Rounds, Tallahassee FL 3/30/06
Hampden County [MA] Medical Society 4/25/06
Boston Medical Center, Family Medicine Grand Rounds 4/25/06
Cooley Dickinson Hospital Northampton MA, Grand Rounds 5/1/06
University of Colorado Family Medicine Grand Rounds 5/3/06
American College of Lifestyle Medicine, Loma Linda CA 5/24/06
Harvard Medical School Lecture to students: Statins 5/30/06
The Regence Group Pharmacy Managers, Portland OR 6/14/06
Alta Bates Hospital, Berkeley CA, Grand Rounds 6/13/06
Harvard Medical School Mind/Body Medical Institute Continuing Medical Education 6/21/06
Tufts Family Medicine Residency 6/23/06
Forum for Behavioral Science in Family Medicine 9/17/06
Biomedical Research and the Law, Hofstra Law School 10/4/06
Sharp Community Medical Group CME Conference 10/8/06
Harvard Medical School, Course on Mind/'Body Medicine 10/20/06
Idaho State University Family Practice Residency 10/26/06
Idaho State University Conference on Health Care 10/26/06

American Public Health Association, panelist : "Drug manufacturers, the FDA, and U.S. health care," Boston, MA 11/7/06

Loma Linda University, School of Pharmacy 11/3/06
Sharp Rees-Steely Community Group CME 11/4/06
Rollins College, Winter Park, FL, 11/13/06
Capital Health Plan, Tallahassee, FL, 11/15/06
National Federation of Women Legislators, Bachelor's Gulch, CO, 11/18/06
University of New Hampshire, Masters in Public Health Program Grand Rounds, Durham, NH, 11/28/06
Washington University, "Pharm-Free Day," St. Louis, MO, 11/30/062007
Panelist at George Washington University: Relations with the Pharmaceutical Industry, Washington, D.C., 1/25/07
Prescription Access Litigation Dinner, Keynote Speech, Washington D.C., 1/25/07
McDougall Program Health Conference, Santa Rosa, CA, 2/2-4//07
Sutter Medical Center, Family Medicine Grand Rounds, Santa Rosa, CA 2/5/07
Renown Medical Center, Grand Rounds, Reno NV., 2/6/07
Gila River Health Indian Community Health Center: "The Growing Gap Between Evidence-Based Medicine and Good Health Care," Sacaton AZ., 2/8/07
Harvard Medical School: "Why Primary Care Don't Get No Respect." 2/13/07
Indian Health Services, National Combined Councils: "Can We Trust the Evidence in Evidence-Based Medicine," San Diego CA. 2/25/07
Harvard Medical School Continuing Education: Mind/Body Medicine Clinical Training, Boston MA. 2/28/07
University of Michigan, Undergraduate class on health policy, Ann Arbor, MI 3/13/07
University of Michigan, Family Practice Grand Rounds, Ann Arbor MI, 3/14/07
University of Texas, Lecture to students and faculty, 3/15/07
DTC Perspectives (National meeting of direct to consumer advertisers) Panel: "What Our Critics Think," Washington DC, 4/10/07

E. Report of Clinical Activities

1982-2002 Family Physician, Hamilton-Wenham Family Practice
1997-2001 Hamilton-Wenham School District Physician

Bibliography

Original Articles

1987 Competition, capitation, and case management: barriers to strategic reform. Milbank Quarterly 1987;65:3: 348-370

2003 Medical Reporting in a Highly Commercialized Environment: A family doctor prescribes eight guiding principles for accurate and fair coverage of research findings. Nieman Reports. 2003; Summer: 54-57

2003 Comments on the MRC/BHF Heart Protection Study. Correspondence. The Lancet. 2003; 362: 745-746

2005 When Health Policy is the Problem (with Bruce Spitz). Journal of Health Politics, Policy and Law, 2005; 30(2):327-366.

2005 The Effect of Conflict of Interest on Biomedical Research and Clinical Practice Guidelines: Can We Trust the Evidence in Evidence-Based Medicine? (With

Barbara Starfield, MD, MPH). Journal of the American Board of Family Practice, 2005; 18:414-418.

2007 Are Lipid-lowering guidelines evidence-based? (With James M. Wright MD, PhD). The Lancet, 2007: 369:168-169.

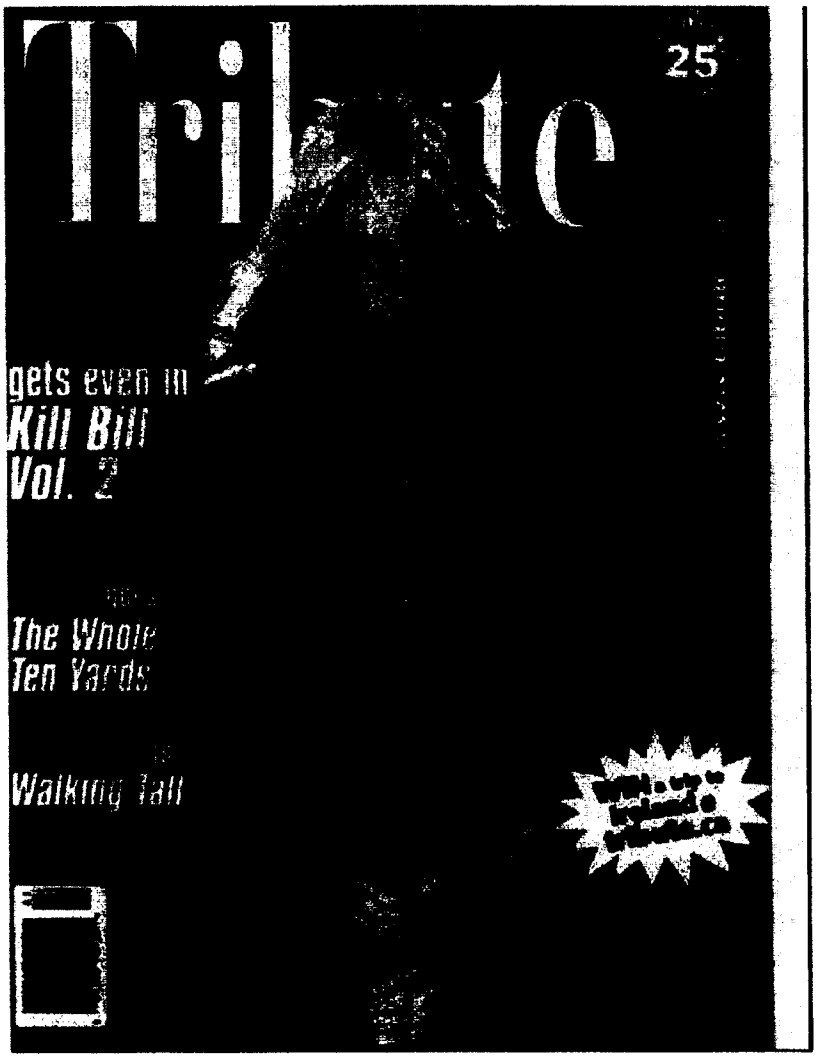
Book

2004 Overdosed America: The Broken Promise of American Medicine. How the Pharmaceutical Companies Distort Medical Knowledge, Mislead Doctors, and Compromise Your Health (HarperCollins, Sept. 2004)

OP-EDS (Major Newspapers)
LA Times Drug Guidelines Fatten Bottom Line 7/25/04
NY Times Information is the Best Medicine 9/18/04
LA Times Physician Know Thy Patient 10/24/04
LA Times Drug Profits Infect Medical Studies 1/7/06
LA Times Healthcare Code Blue 11/3/06
Atlanta Journal Constitution Col-hearted tug fails women 2/2/07

National Media Appearances:
9/30/04 CBS Evening News
Lou Dobbs
CNN Headline News
NPR Radio: All Things Considered
10/1/04 The Today Show
CNN American Morning
10/18/04 FOX News Linda Vester: Bush and Kerry Health Plans
11/04/04 ABC News Vioxx article and editorial in Lancet
11/06/04 CNN "In the Money" DTC advertising
11/18/04 CNN HEADLINE NEWS Vioxx Hearings:
11/19/04 CNN AMERICAN MORNING Vioxx Hearings: Why didn't Doctors know?
11/22/04 FOX LINDA VESTER Merck's role in funding Vioxx research
11/29/04 Lou Dobbs Are We A Nation of Hypochondiracs?
12/05/04 C-Span BookTV: From Collected Works, Brattleboro, VT (Recorded 11-05-04)
12/14/04 (taped)TV Ontario, What to do after Vioxx?
12/17/04 CNN with Betty Nguyen
CNN Wolf Blitzer (interviewed by Mary Snow)
CNBC Closing Bell with Tyler Mathisen
Lou Dobbs Tonight
CNN Headline News
12/18/04 Ron Insana Show (radio)
NBC Nightly News
12/20/04 Fox News: Neil Cavuto
WBUR Radio: On Point
News Night with Aaron Brown
CNN Headline News
NPR Radio: All Things Considered
12/21/04 CNN American Morning
CNN Live
MSNBC Market Wrap with Ron Insana
MSNBC Ron Insana: The Death of a Wonder Drug
12/22/04 The Today Show
CNN Live From
12/26/04 WSJ Report with Maria Bartiromo
1/13/05 MSNBC (Over the Counter Statins)

1/24/05 CBS Evening News: Celebrex
2/18/05 MSNBC Bull's Eye
2/19/05 CNN In the Money
Fox News
CNN Headline News
2/25/05 CNN Prime News
2/28/05 CNN Lou Dobbs LIve
5/27/05 CNN Lou Dobbs Live
CNN Judy Woodruff Inside Politics
5/28/05 Fox with Bob Sellers
7/27/05 Fox and Friends, National
8/15/05 Fox 25, Boston
3/22/06 CNBC Live interview FDA, ADHD drug labeling
6/23/06 CNBC Morning Call: Zocor pricing

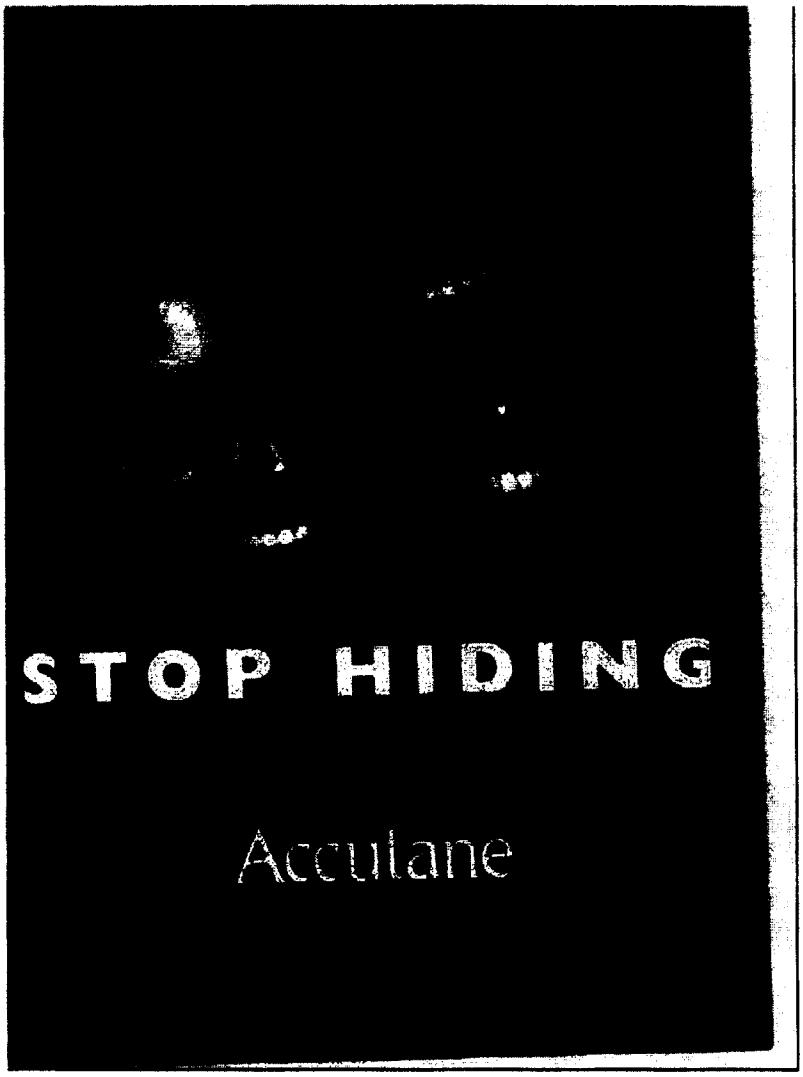


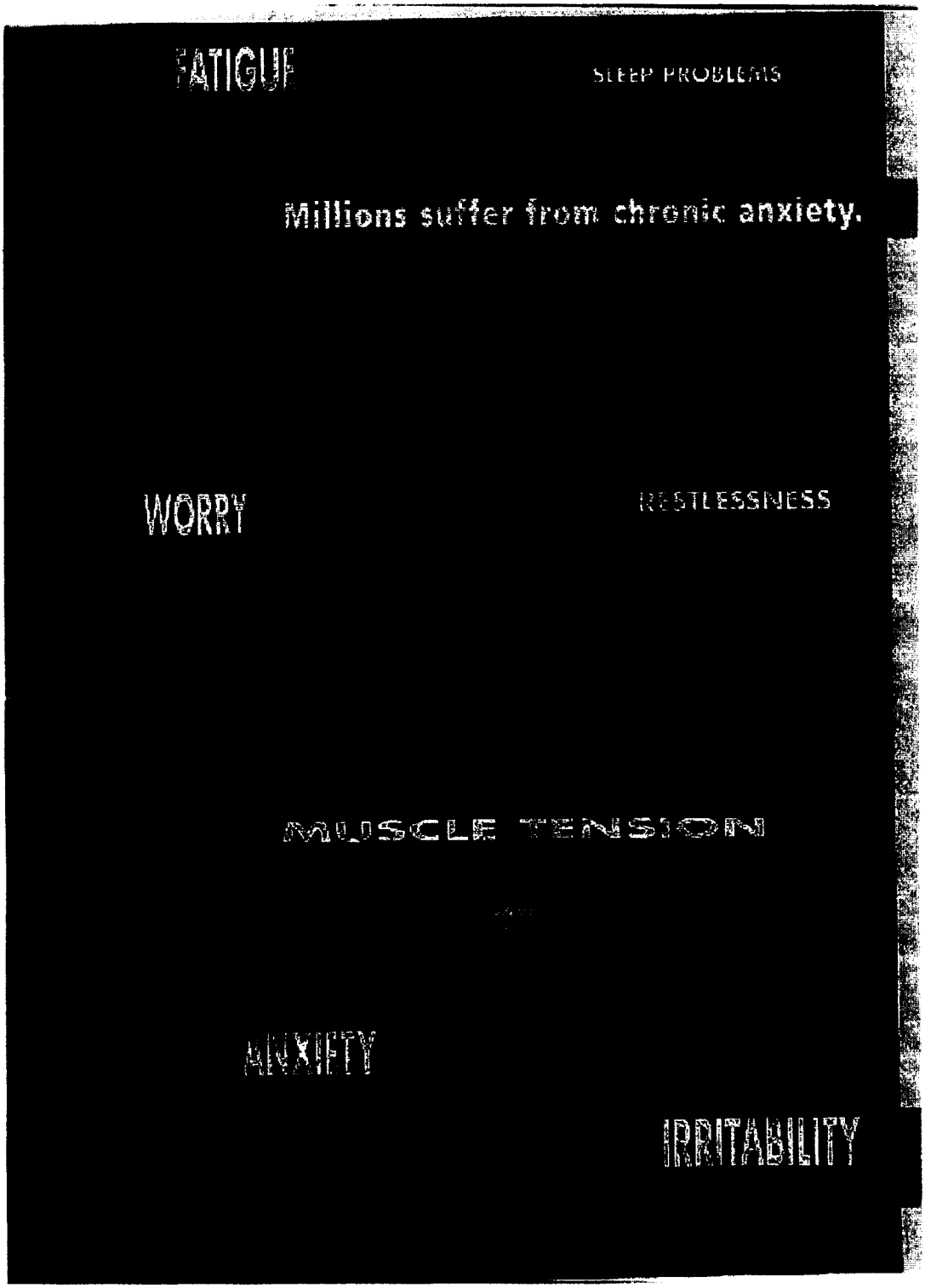
Included as it is the ref (magazine cover for ad above) – 2 teenagers, Accutane promo, discussed in text.

This is Exhibit B-1 referred to in the affidavit of Dr. John Abramson sworn before me this 02 day of May 2007

A COMMISSIONER, ETC.

STEVEN ROBERT McCLENAGHAN
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 8, 2011


STOP HIDING
Accutane



New York Times Magazine, October, 2001

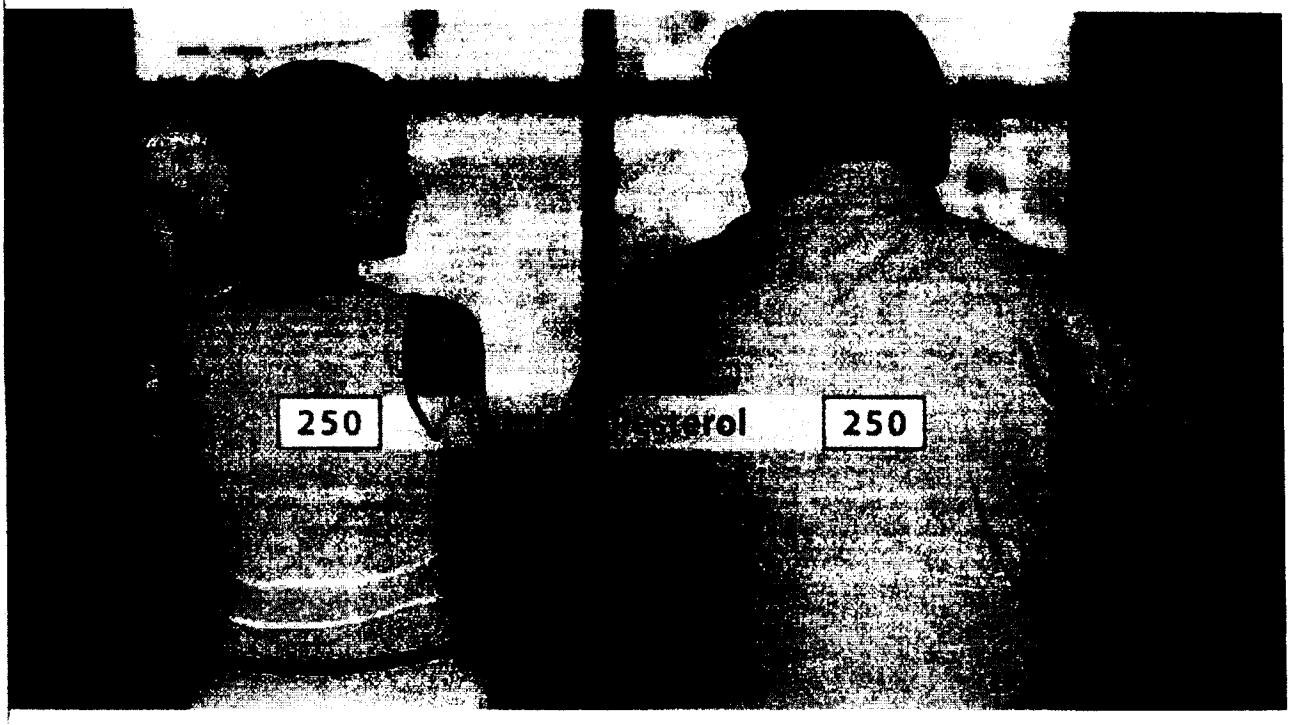
STEVEN ROBERT McCLENAGHAN
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 8, 2011

This is Exhibit B-2 referred to in the affidavit of Dr. John Abramson
sworn before me this 07
day of May 20 07

A COMMISSIONER, ETC.

This is Exhibit....B-3...referred to in the affidavit of ....Dr. John Abramson
sworn before me this .....
day of .....May.....20.07.
A COMMISSIONER, ETC

High cholesterol comes in all shapes and sizes.



Here's a tip. You can be active, thin, young or old. The truth is that high cholesterol may have as much to do with your family genes as food. So, even a strict diet may not be enough to lower it. The good news is that adding LIPITOR can help. It can lower your total cholesterol 29% to 45%.* And it can also lower your bad cholesterol 39% to 60%.* (*The average effect depends on the dose.) More than 18 million Americans have talked to their doctor about LIPITOR. Maybe you should too. Learn more. Find out if the #1 prescribed cholesterol medicine is right for you. Call us at 1-888-LIPITOR. Find us on the web at www.lipitor.com.

LIPITOR®
atorvastatin calcium
tablets
FOR CHOLESSTEROL®

Important information:

LIPITOR® (atorvastatin calcium) is a prescription drug used with diet to lower cholesterol. LIPITOR is not for everyone, including those with liver disease or possible liver problems, women who are nursing, pregnant, or may become pregnant. LIPITOR has not been shown to prevent heart disease or heart attacks.

If you take LIPITOR, tell your doctor about any unusual muscle pain or weakness. This could be a sign of serious side effects. It is important to tell your doctor about any medications you are currently taking to avoid possible serious drug interactions. Your doctor may do simple blood tests to monitor liver function before and during drug treatment. The most commonly reported side effects are gas, constipation, stomach pain and indigestion. They are usually mild and tend to go away.

Please see additional important information on next page.

B-4

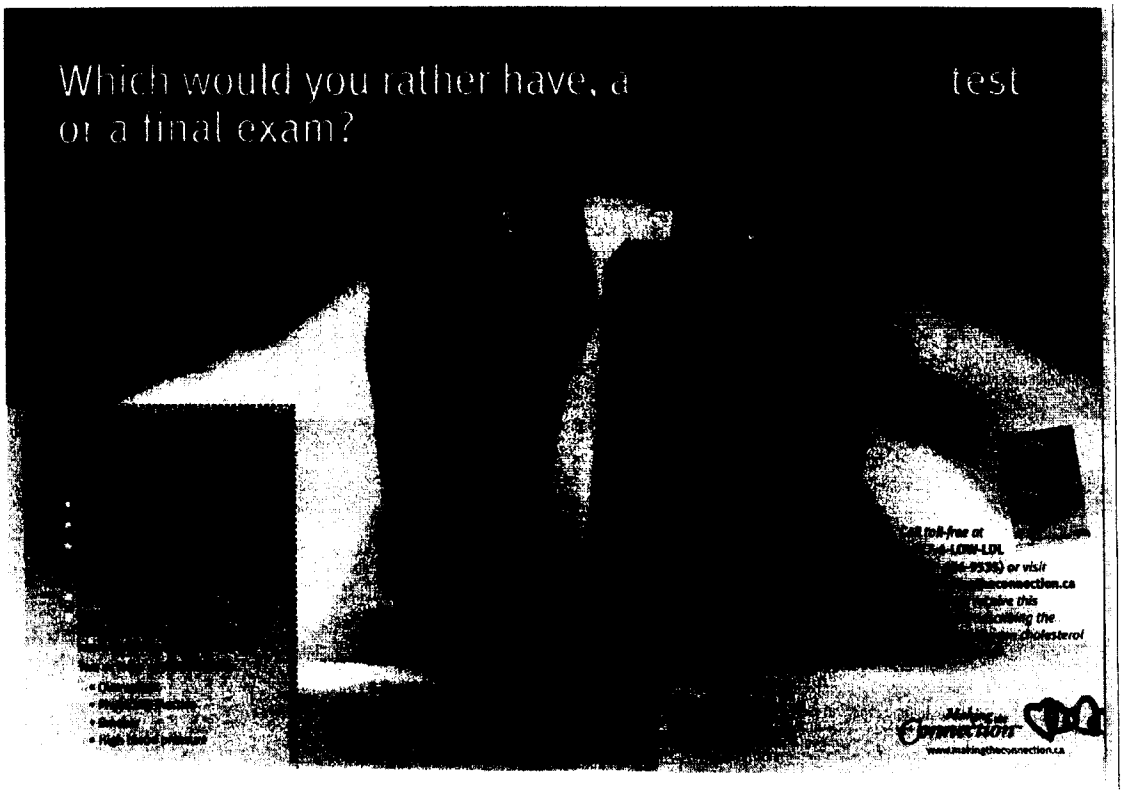
This is Exhibit.....referred to in the affidavit of Dr. John Abramson

sworn before me this 07

day of May 20 07

A COMMISSIONER, ETC.

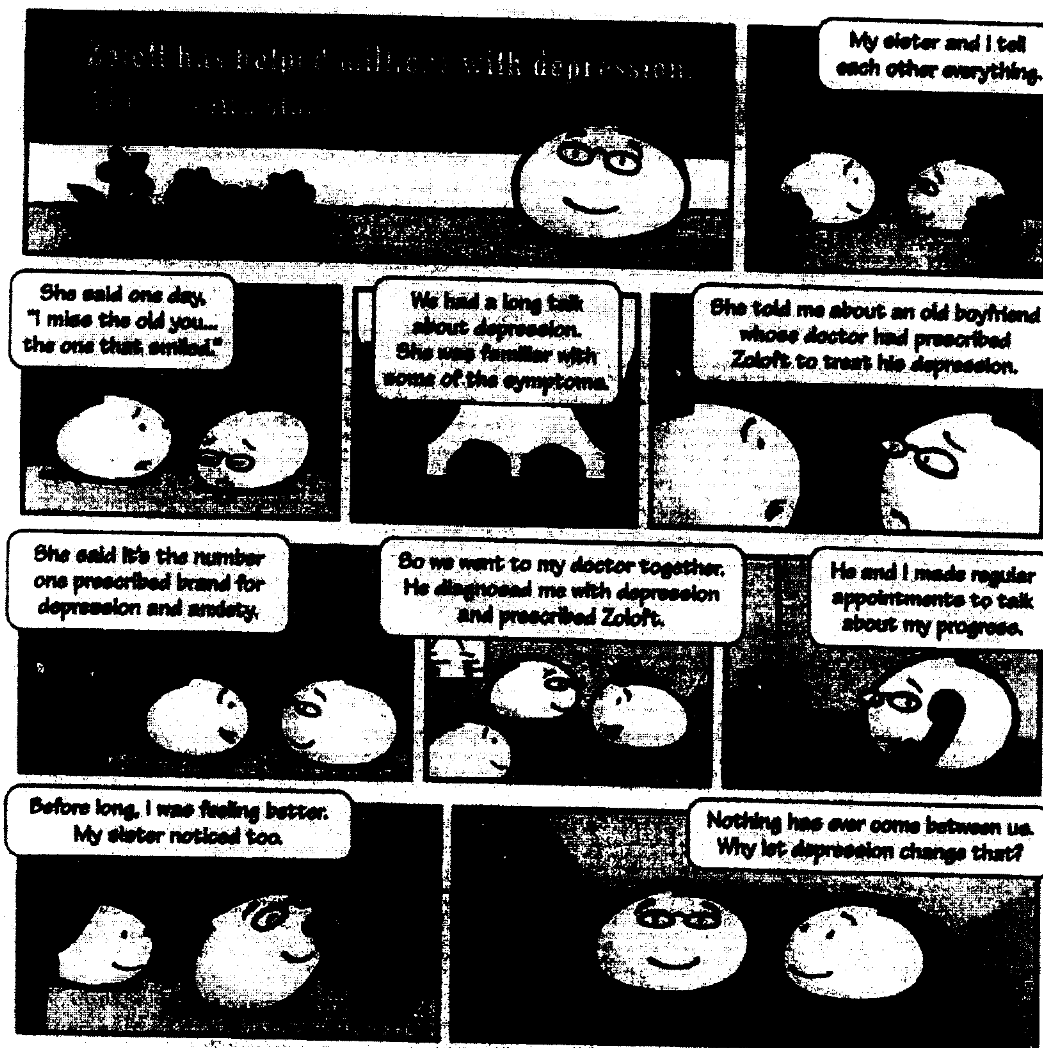
STEVEN ROBERT McCLENAGHAN
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 8, 2011



STEVEN ROBERT McCLENAGHAN
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 8, 2011

This is Exhibit B-5 *referred to in the affidavit of* Dr. John Abramson *sworn before me this* 07 *day of* May 2007

A COMMISSIONER, ETC



Depression is a serious medical condition, which can lead to the risk of suicidal thoughts and behavior. A combined analysis of studies involving 9 antidepressants showed that in people under 18 this risk was 4% for those taking antidepressants compared to 2% for those taking a sugar pill. This risk must be balanced with the medical need. Those starting medication should be watched closely for suicidal thoughts, worsening of depression, or unusual changes in behavior. In children and teens, ZOLOFT is only approved for use in those with obsessive-compulsive disorder.

ZOLOFT is not for everyone. People taking MAOIs or pimozide shouldn't take ZOLOFT. Side effects may include dry mouth, insomnia, sexual side effects, diarrhea, nausea and sleepiness. In studies, few people were bothered enough by side effects to stop taking ZOLOFT. ZOLOFT is not habit forming and is not associated with weight gain.

So talk to your doctor about how ZOLOFT might help you. ZOLOFT comes in 25mg, 50mg, and 100mg tablets. You and your doctor can discuss the dose for you. For more information, please see the following page, call 1-800-6-ZOLOFT (696-5638) or visit ZOLOFT.com.

zoloft (sertraline HCl)

#1 for millions of reasons.
www.zoloft.com

Important Information: ZOLOFT is one of the treatment options that you and your doctor may consider.

Uninsured? Need help paying for medicine? Pfizer has programs that can help, no matter your age or income. You may even qualify for free Pfizer medicines. Call 1-866-706-2400. Or visit www.pfizerhelpfulanswers.com.

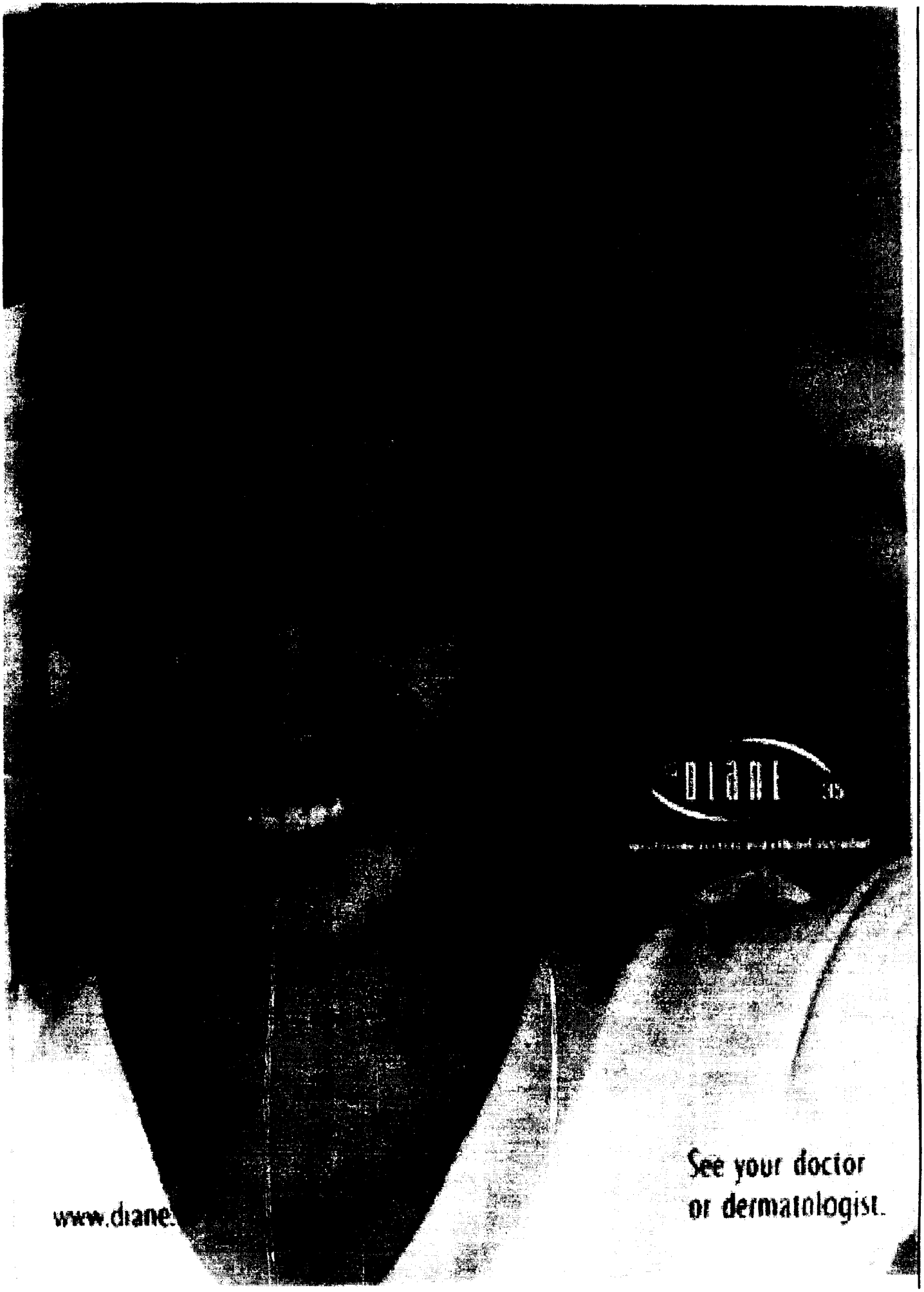
helpful answers

This is Exhibit B-6 referred to in the affidavit of Dr. John Abramson sworn before me this 07 day of May 2007

[signature]

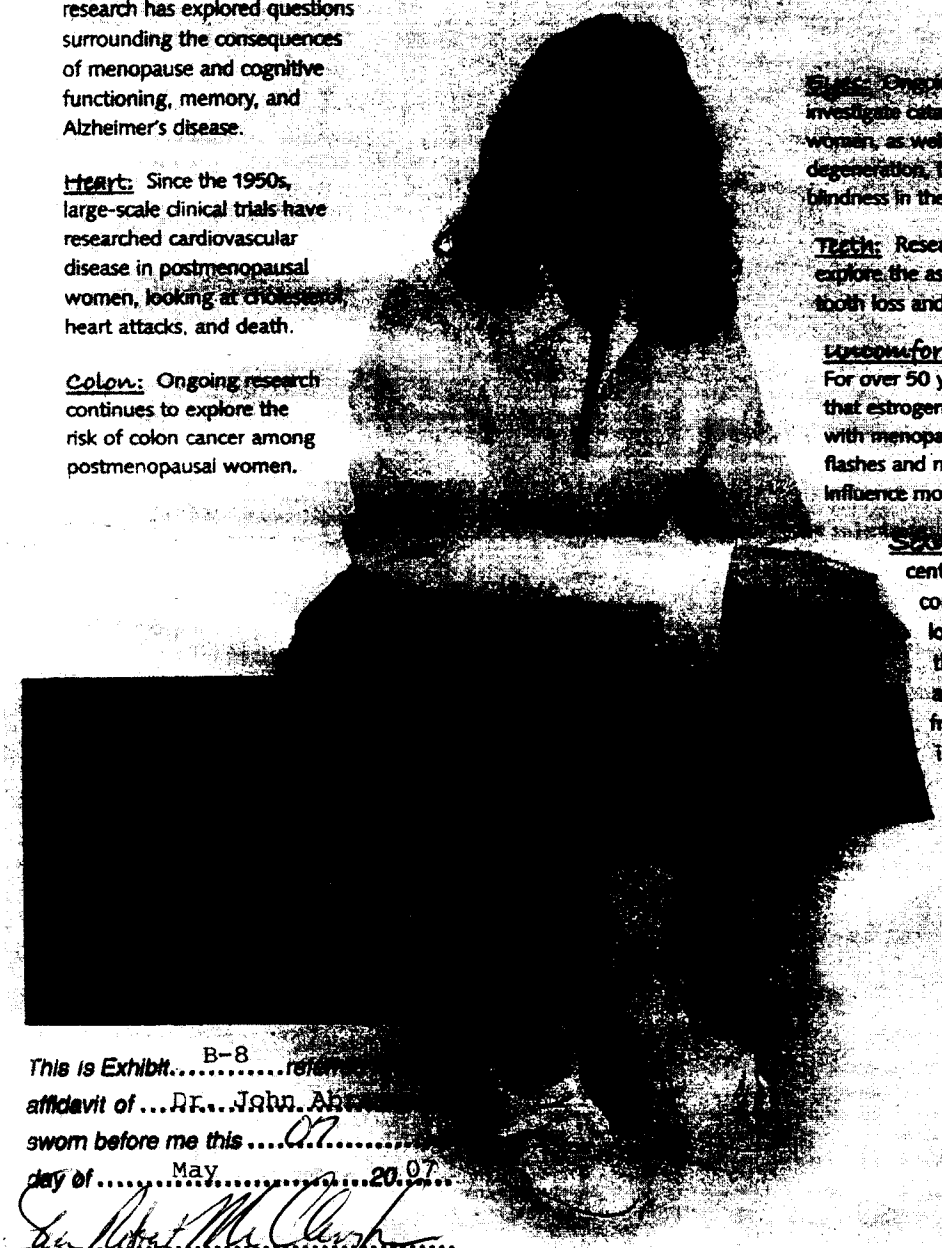
A COMMISSIONER, ETC.

STEVEN ROBERT McCLENAGHAN
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 8, 2011


Diane 35
www.diane
See your doctor
or dermatologist.

"I take an active interest in my health. That's why I asked my doctor about the consequences of estrogen loss at Menopause."

Lauren Hutton



Brain: For the past 10 years, research has explored questions surrounding the consequences of menopause and cognitive functioning, memory, and Alzheimer's disease.

Heart: Since the 1950s, large-scale clinical trials have researched cardiovascular disease in postmenopausal women, looking at cholesterol, heart attacks, and death.

Colon: Ongoing research continues to explore the risk of colon cancer among postmenopausal women.

Eyes: Ongoing research continues to investigate cataracts in postmenopausal women, as well as age-related macular degeneration, the leading cause of blindness in the aging population.

Teeth: Research continues to explore the association between tooth loss and menopause.

Uncomfortable Symptoms: For over 50 years, it's been known that estrogen loss associated with menopause causes the hot flashes and night sweats that often influence mood and sleep.

Sexuality: Half a century of study has confirmed that estrogen loss causes vaginal thinning and dryness and increases the frequency of vaginal infections, which can be uncomfortable and interfere with intimacy.

Bone: Decades of research have proven that estrogen loss decreases bone mineral density and increases the risk of fractures from osteoporosis.

This is Exhibit B-8 referred to in the affidavit of Dr. John Ab... sworn before me this 07 day of May 20 07

A COMMISSIONER, ETC.

STEVEN ROBERT McCLENAGHAN
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 8, 2011

WYETH AYERST
WOMEN'S HEALTH RESEARCH INSTITUTE

This message is sponsored by the Wyeth-Ayerst Women's Health Research Institute, devoted exclusively to the discovery and development of medicines that help women live healthier lives.

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Exhibit C-1

Celebrex Advertisement 2005/2006 - Video

(Included on CD-Rom)

This is Exhibit C-1 referred to in the affidavit of Dr. John Abramson sworn before me this 07 day of May 20 07

A COMMISSIONER, ETC.

STEVEN ROBERT McCLENAGHAN
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 8, 2011

Exhibit C-2

Diane-35 Advertisement Video

(Included on CD-Rom)

STEVEN ROBERT McCLENAGHAN
Notary Public
Commonwealth of Massachusetts
My Commission Expires
December 8, 2011

This is Exhibit C-2 referred to in the affidavit of Dr. John Abramson sworn before me this 07 day of May 20 07

A COMMISSIONER, ETC.

CANWEST MEDIAWORKS INC.
Applicant

- and -

ATTORNEY GENERAL OF CANADA
Respondent

Court File No. 05-CV-303001PD2

ONTARIO

SUPERIOR COURT OF JUSTICE

Proceeding commenced at TORONTO

AFFIDAVIT OF DR. JOHN ABRAMSON

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