Court File No.: 05-CV-303001PD2

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N :

CANWEST MEDIAWORKS INC.

Applicant

and

ATTORNEY GENERAL OF CANADA

Respondent

AFFIDAVIT OF JOEL LEXCHIN

I, **JOEL LEXCHIN**, of the City of Toronto, in the Province of Ontario, solemnly AFFIRM:

1. I am a medical doctor licensed to practice medicine in Ontario since 1977. I have been practicing medicine and prescribing since then. I am a staff physician at the University Health Network, Department of Emergency Medicine, where I have been practicing emergency medicine since 1988.

2. Since 2001 I have also been an Associate Professor on full-time faculty at York University in the School of Health Policy and Management where I teach health policy. I am also an Associate Professor at the University of Toronto in the Department of Family and Community Medicine. I have held that position since 1996. I joined that department in 1988 as a lecturer and became an Assistant Professor in 1991 before I became an Associate Professor.

3. Since the mid 1980s I have been concentrating my researching and writing on pharmaceutical policy, an area of particular interest to me and in which I have become widely recognized. I have been either the sole author or a coauthor of 70 peer reviewed papers in this area.

4. In 1991-92, I attended McMaster in the Design, Measurement and Evaluation graduate program and studied clinical epidemiology and critical appraisal of the medical literature. Through these courses as well as my medical practice and teaching, I have also acquired significant knowledge of and experience in clinical epidemiology to be able to critically evaluate the way that medications are promoted and to be able to make expert assessments as to the safety and effectiveness of medications. I assess promotion by looking at the claims that are made, whether these claims conform to accepted medical evidence, whether the claimed benefits of the drugs result in improved health outcomes for patients, how much prominence is given to safety information and the message that is conveyed through the graphics and statistical material used in the promotion. The evaluation of the safety and effectiveness of medications is done by looking at the strength of the methodology employed in conducting these studies, whether the authors have followed generally accepted criteria in how they have analyzed and reported the results of the trial and whether the studies have taken into account other factors that may have influenced the results.

5. My knowledge of pharmaceutical policy and drug therapy has been recognized provincially, nationally and internationally. I was a member of the

Ontario Drug Quality and Therapeutics Committee (the body that advises the Minister of Health regarding which products to add to the provincial drug formulary) from 1992 to 1994. I have been a coauthor of three editions of a book of prescribing guidelines to general practitioners and the sole author of a similar book for emergency medicine physicians. From 1998-1999 I was the chair of the Drugs and Pharmacotherapy Committee for the Ontario Medical Association.

6. In the area of pharmaceutical policy I have been an expert advisor to the Auditor General of Canada when the Auditor General undertook an audit of the Patented Medicine Prices Review Board (PMPRB) and on a working group set up by the PMPRB to examine several of its policies around drug pricing. I was hired by the New Zealand government to review the policies and procedures of PHARMAC, the agency that manages the drug budget in that country and have also worked for the Australian National Prescribing Service. Finally, I am asked by medical journals around the world to review articles they are considering for publication in the area of pharmaceutical policy. In the past few years I have reviewed more than 30 manuscripts annually.

7. My work in the area of pharmaceutical promotion has been recognized through being invited to attend various workshops conducted by Health Canada including two on the subject of DTCA. I was a member of an ad-hoc task force set up by the Ontario College of Physicians and Surgeons of Ontario to look into the relationship between physicians and the pharmaceutical industry. I was hired as a consultant by the World Health Organization (WHO) to

construct a database of material on pharmaceutical promotion and am currently writing or co-writing two chapters in a manual that the WHO is sponsoring that will be used in undergraduate curricula to teach medical and pharmacy students about pharmaceutical promotion. My full curriculum vitae is attached to this affidavit as Exhibit 1.

8. In this affidavit I will provide evidence with respect to:

- the management of drug risks, including the characteristics that lead to some medications being available over-the-counter while others are sold only on presentation of a prescription and the role of the doctor and other health care professionals as learned intermediaries in assessing the risk and benefit for patients who use prescription drugs;
- how promotion in general, and direct-to-consumer advertising (DTCA) in particular, impacts on issues related to the safety and therapeutic value of prescription drugs, patient behaviour, physician behaviour and the physician-patient relationship;
- the possible alternatives to a complete prohibition of DTCA and my opinion regarding the effectiveness of these alternatives in addressing the harmful effects of DTCA.

9. My evidence and opinions are based on my own knowledge and experience gained through my approximately 24 years as a practicing physician and work in the field of health policy and clinical epidemiology. They are informed by a critical examination of the most important literature on each of the topics that are considered. Throughout the report I will analyze the strengths and weaknesses of the major studies and will present my conclusions based on the material that I have considered. Where I have quoted the opinions of other authors, they are widely accepted as experts in the matters on which they have written, and their statements reflect my own opinion as well. I have attached as

exhibits several reports and articles. In other instances, I refer to sources that are not attached. The references for these are set out in a Bibliography attached as Exhibit 2 to this affidavit. Finally, I have no conflict of interest in this matter.

A. INTRODUCTION

10. Drugs are classified as prescription-only because their risk-benefit ratio requires the expert knowledge of a trained doctor to be able to use them properly. Doctors need to take into account multiple factors in making prescribing decisions on an individualized basis for patients. However, even with that level of knowledge there are a large number of adverse drug reactions ("ADRs") occurring yearly in Canada and that number probably only represents the tip of the iceberg. While many of these reactions are relatively minor, data from the United States suggests that there could be up to 10,000 deaths from ADRs every year in Canada. In my opinion, inserting DTCA into this process treats all patients the same and will bypass the individualized nature of decisions leading to even more adverse outcomes.

11. The great majority of new drugs offer no significant advantages over existing ones. There are significant gaps in the knowledge of the safety profile of new drugs and doctors have limited means to acquire what knowledge there is since safety information is often not fully reported in medical journals. Therefore, to the extent that DTCA speeds up the prescribing and use of new drugs, and later in this affidavit I will provide information showing that it does, in

my opinion, it will not lead to any benefits for most patients but can put them at risk of harm.

12. The example of Vioxx illustrates this concept. Although Vioxx was marketed on the basis that it decreased gastrointestinal bleeding, after it was introduced into Ontario hospital admissions for gastrointestinal bleeding went up by 10%. This was most likely because this drug still carried a small risk of GI bleeding and with a large number of people receiving it, complications were bound to occur. Studies done in the United States and Europe provide compelling evidence that DTCA increases the prescribing and use of drugs that have been advertised.

13. There is no reason to assume that introduction of DTCA into Canada will not have the same consequences, to wit – overuse of new inherently risky medications leading to widespread use of these products in populations where the drug was never tested and unexpected side effects from some of these medications that will not be detected early enough due to the low level of ADR reporting. While some of these unexpected side effects will be relatively trivial others may not be. Over the time Vioxx was available on the American market Merckk spent hundreds of millions of dollars in DTCA of this product. Many medical experts would agree that this promotion was one of the main reasons for the wide-spread use of this product.

14. Out of four papers that have looked at the effects of DTCA on prescribing one showed a benefit and the other three, including the one with the strongest methodology all point to the conclusion that prescribing would become poorer as a result of DTCA. In my opinion, in this situation the precautionary principle should come into play – if there are reasonable grounds for presuming that a policy would have a negative effect, even in the absence of definitive evidence then that policy should not be implemented. This is the situation with DTCA: three studies provide reasonable grounds to believe that prescribing would be negatively affected and therefore DTCA should not be allowed.

15. Canadian and international studies show that patients are highly sceptical about the quality of information in DTCA. Only representatives of the advertising and pharmaceutical industries seem to think that there are few or no problems with the information content of DTCA. These are the groups that stand to gain financially from DTCA. The fact that 80% of people receive the drug that they request may on the surface seem as if patients get appropriate information from DTCA, however that would mean that patients are accurate in both self-diagnosis and treatment selection 80% of the time, a figure that doctors would be hard to match. In my opinion, it is more likely that doctors are giving patients what they want so as not to alienate them. There is no evidence that patients have confidence in DTCA or that it improves their knowledge.

16. Although there are a few measures that show a favourable attitude towards DTCA by doctors, the bulk of the survey evidence from Canada, New

Zealand and the United States indicates a generally negative opinion. The Canadian Medical Association, which speaks for the large majority of Canadian doctors, is on record as opposing DTCA. If DTCA is introduced into Canada most doctors would be opposed to it.

17. A good doctor-patient relationship is essential for appropriate treatment. Doctors and patients need to trust one another so that they can share information and jointly develop a plan for how to deal with the patient's medical problems. The feeling amongst doctors and others, except for the advertising and pharmaceutical industries, is that DTCA has a negative effect on the doctor-patient relationship. Furthermore, about a quarter of patients in the United States state that if they did not get the medication that they requested that they would go elsewhere to get a prescription for the product. Overall, DTCA will, in my opinion, cause a deterioration in the doctor-patient relationship and lead to poorer treatment for patients.

18. In my opinion, none of the three methods used to regulate promotion – industry self-regulation, regulation by independent agencies or government regulation - are well enough resourced and independent enough to be able to adequately control promotion. Attempts to regulate DTCA will not be successful based on experience with the promotion of prescription drugs to physicians and the promotion of nonprescription drugs to consumers in Canada and based on what we have seen in the New Zealand and U.S. experiences with

DTCA. It is my conclusion that since regulation will not work a complete ban on DTCA should be maintained.

B. CLASSIFICATION OF THE RISKS AND SAFETY OF MEDICATIONS

19. Drugs are one of the cornerstones of modern medicine. They achieve this function by modifying various functions in the body but they have both intended and unintended actions which determine their ability to produce positive and negative health outcomes. It is the balance between the benefits and harms of medications as well as the condition that they are intended to treat that determines whether or not they are classified as prescription or nonprescription items. This section of my affidavit will review the grounds upon which this decision is made in Canada.

20. Drug products are put into one of four categories or schedules as outlined on the web page for the National Association of Pharmacy Regulatory Authorities (NAPRA: National Association of Pharmacy Regulatory Authorities 2002):

- Schedule I drugs require a prescription for sale and are provided to the public by the pharmacist following the diagnosis and professional intervention of a practitioner. The sale is controlled in a regulated environment as defined by provincial pharmacy legislation;

- Schedule II drugs, while less strictly regulated, do require professional intervention from the pharmacist at the point of sale and possibly referral to a practitioner. While a prescription is not required, the drugs are available only from the pharmacist and must be retained within an area of the pharmacy where there is no public access and no opportunity for patient self-selection;

- Schedule III drugs may present risks to certain populations in self-selection. Although available without a prescription, these drugs are to be sold from the self-selection area of the pharmacy which is operated under the direct supervision of the pharmacist, subject to any local professional discretionary requirements which may increase the degree of control. Such an environment is accessible to the patient and clearly identified as the "professional services area" of the pharmacy. The pharmacist is available, accessible and approachable to assist the patient in making an appropriate self-medication selection;

- Unscheduled drugs can be sold without professional supervision. Adequate information is available for the patient to make a safe and effective choice and labelling is deemed sufficient to ensure the appropriate use of the drug. These drugs are not included in Schedules I, II or III and may be sold from any retail outlet.

21. Schedule F to the *Food and Drug Regulations* lists the products that fall into Schedule 1, i.e., the ones that can only be sold pursuant to a prescription.[1] The following factors are used by the Therapeutic Products Directorate (TPD) of Health Canada in deciding whether or not products should be listed in Schedule F (Health Canada 2003):

- they require individualized instructions and/or direct practitioner supervision, adjunctive therapy with scheduled drugs or routine laboratory monitoring;
- there exists a narrow margin of safety between the therapeutic and toxic dosages, especially in populations such as geriatrics, children and pregnant/nursing mothers;
- they possess the potential or are known to cause undesirable or severe side effects at normal therapeutic dosage levels;
- they are known by experimental data to induce toxicity in animals but have not been in clinical use for a sufficient period of time to establish the pattern or the frequency of long-term toxic effects in humans;
- they are indicated for serious disease states often misdiagnosed by the public;
- their use may mask other ailments;
- they have contributed to or are likely to contribute to the

[1] Schedule F lists both human and veterinary products.

development of resistant strains of micro-organisms in humans;
- they possess a sufficient dependence or abuse potential that has led or is likely to lead to harmful non-medical use if distribution is not supervised;
- they possess a potentially high level of risk relative to their expected benefits;
- they have a therapeutic effect based on recently elucidated pharmacologic concepts, the consequences of which have not been adequately established.

22. One of the key aspects involved in deciding on prescription-only status is that the drugs are inherently less safe than nonprescription ones and therefore require expert knowledge to be able to use them properly. Usually this knowledge is vested in physicians although other groups of health care professionals such as dentists, podiatrists/chiropodists, optometrists and nurse practitioners may have prescribing privileges. In the case of doctors it takes a minimum of 6 years (4 years of medical school[2] and 2 years of postgraduate training) to acquire this expert knowledge.

23. This knowledge starts with being able to correctly diagnose a medical condition; knowing the probable natural history of the problem and whether it even requires treatment; if treatment is necessary whether pharmacotherapy is more appropriate than other options, choosing between the various medications that are available; and finally incorporating the characteristics of the individual patient into the ultimate decision. Without this knowledge use of these drugs may result in either their not achieving their full therapeutic potential and/or their use having a negative benefit:harm ratio. DTCA

[2] The medical curriculum at the University of Calgary and McMaster University is only 3 years.

has the potential to eclipse all of these considerations because it advocates a single treatment option for all patients regardless of their individual characteristics.

24. Appropriate prescribing means that prescribers should use the knowledge that they have acquired to try to maximize effectiveness, minimize risks and costs and establish effective communication with patients. Using Canadian data for these metrics it is estimated that a considerable percent of prescriptions are inappropriate. I have reviewed the Canadian literature and conclude that problems in all of these areas have been demonstrated and documented. (Lexchin 1998)

25. Adverse drug reactions (ADRs) are one manifestation of this inappropriate prescribing. There are over 10,000 adverse drug reactions reported annually in Canada (Wilson 2006) and the literature suggests that there is significant under reporting of these reactions. British data based on a direct comparison between spontaneous ADR reporting and an observational event monitoring system for a group of more than 44,000 patients suggests that under-reporting may be as high as 98% (Fletcher 1991). One French study estimated that as few as 1 in 24,000 reactions in general were reported to the regional pharmacovigilance centre. Even for serious and unlabelled reactions the reporting figure was only 1 in 4600 (Moride et al. 1997).

26. Moore and colleagues provide one concrete example of that under-reporting: while the FDA received an average of 82 reports annually about ADRs related to digoxin (a heart medication), in a 7-year period there were over 200,000 hospitalizations due to ADRs related to that drug (Moore, Psaty, and Furberg 1998). In the United States adverse drug reactions may cause upwards of 100,000 in-hospital deaths annually (Lazarou, Pomeranz, and Corey 1998). Therefore, even with the expert knowledge that doctors have acquired prescription medications are inherently very risky.

Summary and Opinion

27. Drugs are classified as prescription-only because their risk-benefit ratio requires the expert knowledge of a trained doctor to be able to use them properly. Doctors need to take into account multiple factors in making prescribing decisions on an individualized basis for patients. However, even with that level of knowledge there are a large number of ADRs occurring yearly in Canada and that number probably only represents the tip of the iceberg. While many of these reactions are relatively minor, data from the United States suggests that there could be up to 10,000 deaths from ADRs every year in Canada. In my opinion, inserting DTCA into this process treats all patients the same and will bypass the individualized nature of decision leading to even more adverse outcomes.

C. THERAPEUTIC VALUE OF NEW DRUGS

28. In this section of my affidavit I will examine the added therapeutic value offered by new drugs and also how much is known about the safety profile

when these products appear on the market. Both of these topics are important because DTCA encourages the early use of medications. If most of these drugs are important advances then early use is something that should be encouraged. Similarly, if there is sufficient knowledge about the safety of new drugs then doctors will be in a position to know which patients they are suitable for. On-the-other hand, if most drugs do not offer any therapeutic gains over existing drugs and if their full safety profile is unclear then these drugs should initially be used very cautiously.

29. New drugs can be broken down into two general categories – modifications on existing products and new active substances (NAS). The former are new dosages, new delivery forms or combinations of existing drugs while the latter are products that have never been offered for sale in any form in a given market. What is a NAS in Canada may or may not have the same status in other countries depending on when drugs are introduced into a national market.

30. Changes to the *Patent Act* in 1987 established the federal Patented Medicine Prices Review Board (PMPRB). The main function of the PMPRB is to set a maximum introductory price for new patented medications and to ensure that the prices of these products do not increase any faster than the rate of inflation. In order to achieve the first goal, when a new patented medication is marketed the PMPRB places the product into one of three categories for the purposes of determining its maximum introductory price:

- Category 1 - a new Drug Identification Number (DIN) of an existing or comparable dosage form of an existing medicine, usually a new strength of an existing drug (line extension);
- Category 2 - the first drug to treat effectively a particular illness or which provides a substantial improvement over existing drug products, often referred to as “breakthrough” or “substantial improvement”;
- Category 3 - a new drug or new dosage form of an existing medicine that provides moderate, little or no improvement over existing medicines.

31. Out of 112 NAS marketed in Canada between 2000 and 2004, only 12 or slightly over 10% were Category 2. Six had not been classified and the rest were Category 3 – moderate, little or no therapeutic advances (Patented Medicine Prices Review Board 2005). The National Institute for Health Care Management (NIHCM) has looked at new drug approvals in the U.S. between 1989 and 2000 (Hunt 2002). During that period the Food and Drug Administration (FDA)[3] approved 1035 new drug applications[4]. Overall, 24% of the entire sample was felt to be of sufficient promise that the FDA gave them a priority review. Just 153 or 15% of all the approvals were NMEs that provided significant clinical improvement.

32. The pharmaceutical industry has criticized the figures from both the PMPRB and the NIHCM. In the former case the industry argues that the classifications are for the purpose of establishing an introductory price and only secondarily reflect therapeutic value. In the latter case, the industry points out that the NIHCM left out biologic products and that the NIHCM is financed by

[3] The FDA is the equivalent of the Health Products and Food Branch of Health Canada.

insurance companies whose primary interest is cost containment and would therefore undervalue the worth of new, more costly therapeutic agents.

33. Finally, both sets of determinations are made before the products have actually been in widespread clinical use and are based on pre-marketing trials. Sometimes once drugs are in clinical use they prove to be more valuable than originally thought (Yasuda and Woosley 1992).

34. The third set of figures on therapeutic value avoids all of these criticisms. Since 1981 the independent French drug bulletin, *Prescrire International*, has been assessing the clinical value of new drugs and new indications for existing drugs. By 2004 it made over 3,000 ratings (A review of new drugs in 2004: floundering innovation and increased risk-taking 2005). Table 1 summarizes the data over this 23-year period. The editors of the journal feel that only products in the top 4 categories, 25% of the overall sample, offer any new therapeutic benefit. Out of this group of 774 drugs, 60% fall into the category labelled “minimal additional value”.

35. In conclusion, based on information from three different countries – Canada, France and the United States – at a maximum only a quarter of all new drugs offer an advantage over existing therapies and most of these are only of minimal additional value. True “breakthrough” medications are probably only about 10-15% of the total.

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[4] Of these, 361 or 35% were for new molecular entities (NME) the equivalent of NAS and 674

36. There are a number of different types of trials that can be used to assess medications but the most powerful design is the randomized controlled trial (RCT). The main strength of an RCT is that patients are randomly assigned to take either the new medication or a control, which may be either another drug or a placebo. Randomly assigning patients to one therapy or the other means that there are no biases in deciding who gets what medication. Without randomization there can be systematic differences between people getting the different therapies and these differences can either obscure or magnify the effects of a medication.

37. Often when new drugs appear on the Canadian market the number of published RCTs is extremely limited and the trials that have been published do not compare the new drugs to existing products, are short-term and used small patient groups. Sixteen NAS introduced in Canada between 1992 and 2000 were assessed. For 4 products there were 3 or fewer trials. Only placebo-controlled trials were available for 5 drugs (i.e., these drugs were not compared to other existing products), out of 129 trials only 9% lasted longer than 26 weeks, one-third were shorter than 4 weeks and for 3 drugs no study included more than 100 patients (Lexchin 2002). Therefore, doctors have little independent literature available to them to be able to assess the therapeutic value of these new drugs.

38. Even the trials that have been published in medical journals dealing with drug therapy under-report safety information. Ioannidis and Lau (Ioannidis

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were for incrementally modified drugs (IMD) the equivalent of Category 1 drugs.

and Lau 2001) looked at completeness of reporting of safety information in 192 RCTs in seven diverse medical areas. They found that severity of clinical adverse effects (adverse effects that affected the health of patients) and laboratory-determined toxicity (toxicity determined through the development of abnormal laboratory results) was adequately defined in only 39% and 29% of trial reports, respectively, and only 46% of trials stated how often toxicity resulted in the discontinuation of the study treatment.

Table 1: Therapeutic rating of new drugs in France, 1981-2004

Explanation	**Number of drugs**	**%**
The drug is a major therapeutic innovation in an area where previously no treatment was available.	7	0.23%
The product is an important therapeutic innovation but has certain limitations.	77	2.49%
The product has some value but does not fundamentally change the present therapeutic practice.	223	7.20%
The product has minimal additional value, and should not change prescribing habits except in rare circumstances.	467	15.08%
The product may be a new molecule but is superfluous because it does not add to the clinical possibilities offered by previous products available. In most cases it concerns a me-too product.	2,109	68.12%
Product without evident benefit but with potential or real disadvantages.	87	2.81%
The editors postpone their judgment until better data and a more thorough evaluation of the drug are available.	126	4.07%
Total	3,096	100%

Summary and Opinion

39. The great majority of new drugs offer no significant advantages over existing ones. There are significant gaps in the knowledge of the safety profile of new drugs and doctors have limited means to acquire what knowledge there is since safety information is often not fully reported in medical journals. In my opinion, therefore, to the extent that DTCA speeds up the prescribing and use of new drugs, and later in this affidavit I will provide information showing that it does, it will not lead to any benefits for most patients but can put them at risk of harm. Some of the time that harm will be substantial.

D. DRUG PROMOTION AND ADVERTISEMENTS TO DOCTORS

40. The prescription drug market is unique since the ultimate user is not the person who chooses what to purchase. Doctors have the role of selecting the correct medication for patients amongst the many options and therefore companies direct their promotion in the hope of influencing their choices. The primary purpose of promotion is to increase sales and sales revenue. This section will look at how much money is being spent on promotion and then analyze the accuracy of the material in journal advertisements, the consequences of providing samples to doctors, and the interactions between doctors and sales representatives. Finally, I will examine the relationship between the use of promotion as a source of information and whether doctors choose the most appropriate therapy.

41. There are no up-to-date figures for how much the pharmaceutical industry spends on promotion in Canada but it is possible to make an educated guess. In the U.S. in 2004 total market value was $235.4 billion (IMS Health 2006). In that year the industry spent $23.7 billion on direct promotion (samples, sales representatives and journal advertising)[5] or 10% of sales (IMS Health 2005). Total Canadian sales of prescription drugs in 2004 were $15.9 billion, but $2.0 billion was for generic drugs and generic companies do very little promotion, leaving $13.9 billion sales by brand-name companies (Patented Medicine Prices Review Board 2006). If the U.S. figure of 10% applies then Canadian promotional spending in 2004 was about $1.4 billion. The vast majority of the money was directed at doctors. It should be noted that the $1.4 billion is also only direct costs and does not take into account other factors such as the cost of unnecessary doctors' visits and additional laboratory or imaging tests.

42. There does not seem to be any doubt that promotional spending drives up sales as judged by return on investment. In the U.S. for the top 63 largest revenue brands (sales of $500 million and greater) each extra dollar spent on detailing and journal advertising returned $11.6 and $12.2, respectively (Wittink 2002).

[5] The total leaves out money spent on direct-to-consumer advertising, events sponsored by companies, payment for satellite symposia (company sponsored talks attached to meetings of medical societies), clinical trials designed mainly to get doctors to start prescribing a new drug, gifts to doctors and paying for doctors to attend meetings and conferences. Therefore, the 10% figure should be regarded as a minimum.

43. Table 2 gives spending on the top 10 most heavily promoted products in Canada in 2000 (CBC-TV Disclosure 2002).[6] Promotion tends to concentrate on the newest medications and the ones that have the largest target populations or that will be used for extended periods of time. These are the products that are expected to produce the most sales revenue.

44. It is important to note that the newest drugs or the ones that will be used the most are not necessarily the ones that produce the greatest medical benefits. As was discussed in the previous section, to the extent that promotion focuses on new drugs it encourages the use of drugs with incomplete safety profiles. Of the top 10 most heavily promoted drugs in Canada in 2000 (Table 2) two – Vioxx and Baycol – were subsequently removed from the market because of safety concerns.

Table 2: Drug promotion in Canada – top 10 products in 2000

Brand name	Promotional expenditures ($000)	Number of ad pages in Canadian medical journals	Number of visits by sales representatives to doctors offices (000)	Number of samples of medications left with doctors (000)
Vioxx	6,286	1,090	48	1,060
Celebrex	6,064	613	77	988
Effexor	5,262	974	48	410
Lipitor	4,385	559	65	513
Baycol	3,952	361	54	281
Celexa	3,758	454	35	363
Norvasc	3,689	544	47	351
Avandia	3,650	264	48	170
Paxil	3,640	356	54	281
Atacand	3,624	528	38	202

[6] It is not clear what categories of promotion are included in the amount of money reported spent on each product.

45. There have only been a couple of systematic analyses of the quality of advertising in Canadian medical journals. One looked at references in the ads and assessed whether or not the statement in the ads fairly reflected what was in the cited article and also examined the methodological quality of the material being referenced. Although the statements in the ads reflected what was said in the references the methodologic quality of the references was not judged to be acceptable. Ads tended to use reviews that were of poor quality and a variety of unreferenced secondary sources of data (Lexchin and Holbrook 1994). To accept the use of poor quality references means that it would become the responsibility of the clinician to consult each reference in an advertisement in order to determine its quality and appropriateness. Such an endeavour would be time consuming and detract from the other activities expected of a busy clinician. In addition, 40% of the references to “data on file”, that is, unpublished data in the possession of the company marketing the drug, was not sent despite a request for such information.

46. The second study looked at whether or not journal ads reported benefits from drugs as a relative risk reduction (RRR), absolute risk reduction (ARR) or number needed to treat (NNT). A RRR is the percent reduction in the risk of targeted complications between two groups: a drop in mortality from 50% to 25% would be a RRR of 50%. An ARR is the absolute percent difference in the risk of targeted complications between two groups: a drop in mortality from 50% to 25% would be an ARR of 25%. The NNT is the number of patients that

have to be treated in order to prevent one complication of their disease: a drop in mortality from 50% to 25% would be a NNT of 4 (100/ARR).

47. Physicians are more reluctant to prescribe drugs when results are reported as ARR or NNT than when they are given as RRR. Out of 22 ads, in 11 cases only RRR was used, in two RRR was used but it was possible to calculate an ARR or NNT and in 9 cases no measure was reported but it was possible to calculate a RRR, ARR or NNT from the data given in the ad (Lexchin 1999). Reporting results only as RRR may have encouraged undue prescribing of the advertised drugs.[7]

48. Ads from medical journals in other developed countries had significant problems in the way that they presented information in graphs and charts (Cooper et al. 2001); in not using strong scientific evidence to support claims made (Lankinen et al. 2004; Loke, Koh, and Ward 2002); in a lack of balance between the benefits and risks cited for the products (Rothermich, Pathak, and Smeenk 1996), and in the types of claims made about economic benefits (cost-effectiveness, improved productivity) provided by the drugs (Neumann et al. 2002).

49. How much influence sampling has on prescribing behaviour is unclear. One systematic review identified 23 papers on the topic published between 1986 and the end of 2001. All of the studies suffered from significant

methodologic problems; all studies were observational and none were designed to test specific hypotheses or to test interventions designed to change practice relevant to sampling (Groves, Sketris, and Tett 2003).

50. Although a number of these studies found that the availability of samples influenced the choice of medication, only two looked at whether the choice was more or less appropriate. One concluded that the presence of samples may lead doctors to prescribe a drug that was not their preferred choice (Chew et al. 2000) while the other found that the effect of samples on prescribing of preferred[8] nonsteroidal anti-inflammatory drugs was statistically significant but small (Brewer 1998).

51. Since the publication of the review an additional two studies have looked at the effect of samples on prescribing appropriateness. One before-and-after study looked at whether family practice residents and staff changed their prescribing for high blood pressure after their clinic stopped taking samples and found a marked improvement in first-line prescribing once samples were discontinued (Boltri, Gordon, and Vogel 2002). The second study was a randomized trial comparing two groups of internal medicine residents. In the group that did not use samples there was a trend to use of less expensive agents (Adair and Holmgren 2005). None of these studies have been done on a Canadian sample of doctors.

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[7] Since publication of this study journal ads in Canada have been required to either report results as ARR or NNT or to provide the data necessary to calculate one of these measures.

52. There are currently over 5000 sales representatives employed in Canada (IMS Canada 2003). There have not been any Canadian studies on the interactions between pharmaceutical representatives and doctors. Studies in other developed countries have shown that sales reps fail to spontaneously mention safety information. Table 3 summarizes surveys in Australia, Finland and the United States (Lexchin 1997) while Table 4 documents the results of an ongoing survey of French doctors who see sales reps and then fill out a questionnaire after the interaction (Performance of sales representatives in France: still bad 2003).

Table 3: Nature of information provided by sales representatives to physicians

		Finland		United States	Australia
Year		1975	1986	1993	1992-4
No. of interactions observed		69 (%)	46 (%)	13 (%)	33* (%)
Item spontaneously mentioned by sales rep	**Indications**	91	90		73
	Generic name	78	62		45
	Price	35	29		12
	Side effects	29	27		27
	Contraindications	27	25		0
Incorrect statements (out of total number of statements)				11	
Details containing incorrect statement				62	39

*Number of drugs detailed

[8] Preference was based on cost, efficacy and side effects.

Table 4: Survey of interactions between sales representatives and French doctors

Observed item	1998-99 (% of time)	1999-00 (% of time)	2000-01 (% of time)	2001-02 (% of time)
Do indications match those on product monograph	70	69	64	73
Does dose regimen match that on product monograph	88	86	85	85
Side effects mentioned spontaneously	22	13	9	14
Contraindications mentioned spontaneously	17	18	10	22
Drug interactions mentioned spontaneously	15	14	8	17
Given nature of drug should detailer have mentioned above information (side effects, contraindications, drug interactions)	79	81	87	85
Detailer willing to answer questions	53	44	32	46
Was detailer convincing	19	14	6	9
Pressure to prescribe drug	35	46	54	47

53. What is striking about these two tables is the selective nature of the information that sales representatives spontaneously give to doctors – safety information is offered much less often than information favourable to the drug.

54. The effects of different forms of promotion to doctors on how well they prescribe has been examined in a series of studies in Belgium, Finland, Netherlands, United Kingdom and the United States ranging back to the early 1970s. With the exception of a single study in Finland all of the rest have shown a correlation between more use of promotion as a source of information about pharmacotherapy and less appropriate prescribing. This correlation persists

regardless of the metric used to measure prescribing behaviour. There are limitations to this literature:

> They [the studies in question] can only provide circumstantial evidence for a causal link between promotion and individual prescribing. Other doctor characteristics, such as attitudes to risk, beliefs about clinical experience and evidence, views of new technologies, and academic inclination or ability maybe behind these results. For example, doctors who believe that their clinical experience is more important than scientific evidence may be less likely to respond to evidence presented in journals, and therefore be more dependent on other sources of information such as promotion, and less likely to prescribe rationally (i.e., according to the evidence). Alternatively less academically inclined doctors may not read journals, may rely on advertising because it is very accessible, and may also prescribe in less than optimal ways. The main problem with these studies is that they cannot show that doctors who report relying on promotion would prescribe differently or more rationally, if they did not rely on promotion (Norris et al. 2005).

Summary and Opinion

55. Drug companies currently spend at least $1.4 billion on promotion to doctors. The drugs that are promoted are the ones that generate the most revenue not necessarily the ones that produce the greatest medical benefit. There are significant biases in information in journal advertising and in information acquired through interactions between sales reps and doctors. In the latter case safety information is systematically downplayed. Use by doctors of any of the three main methods of promotion – journal ads, interactions with sales reps and sampling – for information about prescribing and medications is associated with poorer quality of prescribing. Overall, promotion contributes to the cost of drugs but produces adverse effects on prescribing. Poorer prescribing is most likely to lead to poorer outcomes for patients.

E. EFFECTS OF DIRECT-TO-CONSUMER ADVERTISING

56. If DTCA is introduced into Canada it can be expected to impact on all aspects of pharmaceutical use. In this section of my affidavit I will review the relevant literature in three areas and will draw conclusions about the nature of that impact. The three areas I will examine are: impact on the drug safety system; impact on prescribing and patient outcomes; and impact on the behaviour of doctors and patients and the effect on their relationship.

1. Impact on Canada's Drug Safety System

57. Clinical trials conducted before a drug is marketed typically enroll a very selected group of patients, often leaving out the elderly (Mitka 2003) and women (Rochon, Berger, and Gordon 1998), and only including people with a clear diagnosis. Once a drug is approved and enters the real world it will be prescribed and used in patient populations that were never studied. Problems that were not seen in the initial cohorts often come to light or adverse effects that were rare in trials turn out to be common in practice. Although rofecoxib was marketed on the basis that it decreased gastrointestinal (GI) bleeding, after it was introduced into Ontario hospital admissions for GI bleeds went up by 10% (Mamdani et al. 2004). This was most likely because these drugs still carried a small risk of GI bleeding and with a large number of people receiving them complications were bound to occur.

58. The number of patients in pre-marketing trials means that relatively rare but serious adverse reactions can be missed; for instance, in order to be 95% sure of seeing an event at a rate of 1:1000, 3000 people must be studied. This number is about 60% of the total of all patients studied before a drug reaches the market (DiMasi, Hansen, and Grabowski 2003) meaning that in general no adverse event that occurs in fewer than 1:1800 people will be detected.

59. Once a drug has been authorized for sale and is marketed most new safety information comes from reports of adverse drug reactions (ADR). As was described above in the section about drug risks and safety, ADRs are significantly under-reported.

60. Because knowledge about the safety profile of new drugs is limited, under ideal circumstances new drugs should be introduced into the population slowly enough that new and unexpected safety problems can be detected early and measures undertaken to try and minimize negative consequences from the drug.[9] Ideal circumstances would mean that doctors would have easy access to all of the available literature about a drug; there would not be any pressure on them to prescribe the product either from promotion directed at them or from patients; patients would have been properly assessed and would have tried and

[9] There are times when a new drug might have to be widely disseminated, e.g., new effective antivirals in case of flu pandemics.

failed existing therapies; and patients would be closely monitored for both expected and unexpected side effects from the drug.

61. However, heavy use of DTCA violates at least one of the conditions laid out above. DTCA has been shown to lead to very rapid uptake of new drugs. A recent systematic review[10] of the DTCA literature found three studies that had looked at the effects of DTCA on drug sales. This systemic review by Gilbody, Wilson, and Watt, "*Benefits and harms of direct to consumer advertising: a systematic review*" in *Qual. Saf. Health Care* 2005, is attached as Exhibit 3 to this affidavit. The authors state:

> Two interrupted time series studies conducted in the US found a significantly increased trend in the prescribing volume of drugs that had been the subject of DTCA campaigns. The effect of DTCA seemed to both increase the number of new diagnoses of a condition and tended to increase the proportion of prescriptions specifically for the advertised drug. For example, Zachry et al found that advertising budgets for cholesterol lowering drugs increased year on year during the 1990s, and that every $1000 spent advertising cholesterol lowering drugs was associated with approximately 32 extra people being diagnosed with hyperlipidaemia and 41 advertised cholesterol lowering drugs being prescribed. Similarly, Basara found that a specific campaign for a migraine treatment (sumatriptan) was associated with a marked increase in sales over the first month of a campaign (p,0.0006) which, if extrapolated across the US market, was associated with $11.5 million in sales annually.
>
> A European study examined the impact of a mass media campaign sponsored by a pharmaceutical company to increase awareness of and treatment for a fungal nail condition (onchomycosis). A ban on product specific DTCA prevented the company naming their product, but the overall ''awareness campaign'' was associated with both an increase in new prescriptions and the market share of the company's specific antifungal agent (increased prescribing volume during the period of the

[10] A systematic review is a structured search for literature based on pre-established criteria that is undertaken to answer a specific question. It differs from a non-systematic review primarily in its explicit attempt to remove sources of bias from the ways in which the material is found and interpreted.

campaign from 6.50 prescriptions per 1000 person years (95% CI 6.33 to 6.66) to 15.2 (95% CI 13.5 to 16.9)).

62. In the U.S. new drugs are often heavily promoted through DTCA. (See Table 5 (Arnold 2005)). In 2001, Merck spent US $135 million on DTC advertising of Vioxx (Yuan and Duckwitz 2002) helping to contribute to its use by 20 million Americans and annual sales of US $2.5 billion. However, many of the people who received rofecoxib (and other COX-2s) were at low risk for the complications from traditional NSAIDs and could have safely used these much less expensive products. According to estimates, this inappropriate use accounted for more than 63% of the growth of COX-2s between 1999 and 2002 (Dai, Stafford, and Alexander 2005). At the same time, it is also undoubtedly true that a relatively large number of people who received these drugs were elderly and therefore at high risk for cardiovascular problems. As a result of this widespread use, partly fueled by DTCA, there was an estimated 88,000-140,000 possible excess cases of serious coronary artery disease in the U.S. (Graham et al. 2005).

Summary and Opinion

63. Widespread early use of new drugs can lead to more harm than benefit. Studies done in the United States and Europe provide compelling evidence that DTCA increases the prescribing and use of drugs that have been advertised. There is no reason to assume that introduction of DTCA into Canada will not have the same consequences, to wit – overuse of new inherently risky medications leading to widespread use of these products in populations where

the drug was never tested and unexpected side effects from some of these medications that will not be detected early enough due to the low level of ADR reporting. While some of these unexpected side effects will be relatively trivial others may not be.

Table 5: DTCA advertising in the United States – top 20 products in 2004 (January to November)

Rank	Brand	Manufacturer	Amount spent ($ millions)
1	Nexium	AstraZeneca	226.0
2	Crestor	AstraZeneca	193.2
3	Cialis	Eli Lilly	152.6
4	Levitra	Bayer/GlaxoSmithKline/ Schering-Plough	142.0
5	Zelnorm	Novartis	122.0
6	Prevacid	TAP Pharmaceuticals	118.9
7	Flonase	GlaxoSmithKline	118.4
8	Singulair	Merck	107.7
9	Celebrex	Pfizer	104.4
10	Lipitor	Pfizer	103.8
11	Welbutrin XL	GlaxoSmithKline	99.0
12	Plavix	Bristol-Myers Squibb/Sanofi-Aventis	98.1
13	Allegra	Sanofi-Aventis	95.7
14	Viagra	Pfizer	95.6
15	Valtrex	GlaxoSmithKline	92.0
16	Zocor	Merck	87.0
17	Lamisil	Novartis	84.4
18	Zyrtec	Pfizer/UCB Pharma	84.1
19	Zoloft	Pfizer	83.7
20	Elidel	Novartis	82.0

2. Effect of DTCA on Prescribing and Patient Outcome

64. Four papers have been published that analyze prescribing in response to DTCA: one is a survey, two are observational studies and one is randomized controlled trial (RCT). The concept behind an RCT has already been explained. An observational study is one where a group of people who have

been exposed to something (a drug, something in the environmental, the purchase of some object) are followed to see how the exposure affects them both positively and negatively. A survey is a collection of opinions from a group of people about a particular question. RCTs yield the highest quality of evidence, observational studies give an intermediate quality and surveys the lowest quality.

65. In New Zealand, Toop and colleagues (Toop et al. 2003) surveyed general practitioners asking them whether as a result of a patient's request they had switched to/started medication with an advertised drug which they felt offered little benefit over treatment they would ordinarily use. They received a response from 50% of the country's GPs, 44% of whom either strongly or slightly agreed with that statement compared to 42% who slightly or strongly disagreed. Only 3% of respondents felt DTCA improved the quality of their prescribing.

66. As with all surveys, this one is subject to social acceptability bias. Social acceptability bias occurs when respondents provide answers that they think are the "correct" ones rather than the way they actually think. Another problem with surveys is that those who respond may differ in some fundamental way from those who do not. However, these possible weaknesses need to be balanced against the fact that 84% of those responding believed that DTCA did not improve their prescribing. It is difficult to believe that all of the non-respondents would have felt differently.

67. Mintzes and colleagues (2003) carried out a cross-sectional observational study involving patients and primary care practitioners in Vancouver and Sacramento. They asked doctors “if you were treating another similar patient with the same condition, would you prescribe this drug?” If doctors prescribed when patients had requested a drug that had been subject to DTCA their response was ambivalent 50% of the time (they “possibly” or “unlikely” would have prescribed the same drug). For drugs not requested by patients they were only ambivalent 12% of the time.

68. As a cross-sectional survey the results from this study should only be regarded as exploratory. Furthermore, the physicians who agreed to cooperate may not be representative of primary care doctors in general in terms of their response to requests for drugs subject to DTCA. The report on this survey which appeared in the *Canadian Medical Association Journal*, Sept. 2, 2003; 169(5) is attached to this affidavit as Exhibit 4.

69. The other observational study focused on 6 antidepressants in the population of beneficiaries of a group of large self-insured companies (Donohue et al. 2004). The authors looked at antidepressant prescribing during periods when the amount of money spent on DTCA for this group of drugs was at different levels. They examined two outcomes: whether a prescription for one of the study medications was written within 60 days of the diagnosis of depression and if an antidepressant was prescribed did patients receive an appropriate duration of treatment with the drug. The authors noted:

> Individuals diagnosed with depression during periods when class-level antidepressant DTCA spending was highest … had 32% higher relative odds of initiating medication therapy compared with those diagnosed during periods when DTCA spending was lowest (*P* 0.0001)… Class-level DTCA spending on antidepressants had a small positive effect on the duration of antidepressant use, whereas DTCA spending for the specific medication taken by an individual had no effect on treatment duration.

70. This study has a number of limitations. The main one is that it was an uncontrolled before and after study (i.e., there was no unaffected population to act as a comparator) and therefore could not account for other factors that may have altered prescribing behaviour. A second significant limitation was that the authors grouped together patients with a number of different diagnoses: major depression current episode; major depression recurrent episode; depression not elsewhere classified; dysthymia, anxiety depression or prolonged depressive reaction. Antidepressant treatment may not be appropriate in all cases but the authors did not report on variations in antidepressant use in the different classes of patients.

71. The randomized trial by Kravitz et al (2005) employed standardised patients (SPs) who were trained to present symptoms of either major depression or adjustment disorder with depressed mood and then visited the offices of primary care physicians and made a brand-specific drug request, a general drug request or no request. In the case of major depression drug therapy was judged appropriate while in the latter instance there is no professional consensus about the need for immediate treatment with medications as opposed to watchful waiting.

72. The results showed that patients presenting symptoms of major depression and asking for a specific drug were much more likely to be prescribed an antidepressant and get delivery of acceptable initial treatment than those making no request. However, a general non-commercially driven request for an antidepressant produced just the same effect. Moreover, for patients with symptoms of adjustment disorder prescription rates increased several fold following either a brand-specific or general request. Therefore, according to the authors, while it is possible that DTCA may have positive effects when the target condition is serious and the treatment is very safe, effective and inexpensive, DTCA is likely to be harmful when the target condition is trivial and the treatment is relatively perilous, ineffective or costly.

73. In my opinion this study has a relatively strong methodologic design. The main limitation is that the investigators could not be sure that DTCA produces the same kind of behaviour in actual patients as what was portrayed by the SPs. The report of the study which appeared in the *Journal of the American Medical Association*, April 27, 2005-Vol 293, No. 16 is attached as Exhibit 5 to this affidavit.

74. One paper purports to look at the health effects of DTCA (Weissman et al. 2003). The study in question reports on the results of a U.S. national telephone survey of consumers in which consumers were asked about

visits to their doctors during which DTCA prompted them to discuss their health. The authors report:

> … that a sizable portion of patients with DTCA visits reported seeing their physicians for clinically important conditions and that many visits resulted in new diagnoses. Some of the most common new diagnoses that were discovered as a result of these visits—high cholesterol, hypertension, diabetes, and depression—are often underdiagnosed and undertreated in the general population… Second, we found that DTCA visits resulted in health care actions taken on behalf of patients that went beyond the expected prescribing of drugs, both advertised and not. Third …we did not detect widespread adverse effects of DTCA based on self-reported health status.

75. The authors note that because of the ubiquity of DTC ads in the U.S. finding a control group that was not exposed to advertising would be exceedingly difficult. However, as Bodenheimer (Bodenheimer 2003) notes in his critique of this study, without such a control group the conclusion that it was the DTCA-inspired visits that lead to the discovery of new diagnoses cannot be made with any certainty. Second, because this was a survey of patients and not their doctors it is impossible to know if the new diagnosis was incidental or central to the DTC ad that patients viewed. The new diagnosis could have been the result of a conversation that had nothing to do with the original reason for the visit. Finally, it is questionable whether or not patients could accurately identify adverse health effects due to DTCA. The article does not give the period of time between the visit to the doctor and when the survey was done and the elapsed time between the two events may have been too short for any negative health outcomes to become manifest.

76. Avorn (Avorn 2003) provides additional reasons to question the findings of the article. The authors of the article classified patients into two groups: those for whom DTCA was one of the two most important sources of information that influenced them to see their doctors (high DTCA influence) versus all other patients (low DTCA influence). Avorn points out that those with high DTCA influence were not more likely to have a new health concern discussed or a new diagnosis made compared to the low DTCA influence. When new diagnoses were made, they were less likely to be confirmed by a doctor in those with high DTCA influence than in those with low DTCA influence. Both of these findings are in contradistinction to one of the principles of epidemiology – the dose response effect – the higher the dose the stronger the response.

Summary and Opinion

77. The paper by Weissman and colleagues that showed positive effects of DTCA on health outcomes cannot be dismissed but its methodologic weaknesses and the contradictory findings mean that it cannot be accepted without confirmation by methodologically stronger research. The other three papers, including the RCT by Kravitz, all point to the conclusion that prescribing would become poorer as a result of DTCA. It is my opinion as a physician and health policy specialist, that in this situation the precautionary principle should come into play – if there are reasonable grounds for presuming that a policy would have a negative effect, even in the absence of definitive evidence, then that policy should not be implemented. This is the situation with DTCA: three

studies provide reasonable grounds to believe that prescribing would be negatively affected and therefore DTCA should not be allowed.

3. Effect of DTCA on Patient Behaviour, Physician Behaviour and the Physician-Patient Relationship

78. Virtually all of the literature in these areas is dependent on survey results rather than direct behavioural observation and must be viewed with some scepticism. Questions can be raised regarding how representative the surveys are and there is also the ever-present concern about social acceptability bias (respondents providing what they believe is the “correct” response rather than what they actually believe) in survey responses.

a. Patient Attitudes and Behaviour

79. The key questions here are how do patients feel about DTCA – do they trust the information that they are being given and what effect does DTCA have on their subsequent behaviour in terms of seeking medical care and taking medications. If patients are distrustful of the information in DTCA then it is unlikely that it would be useful to them.

80. The 2003 study by Mintzes and colleagues attached as Exhibit 4 has already been discussed with reference to the effects of DTCA on physician prescribing. 87.4% of the Vancouver patients had seen at least one DTC ad in the past year and 30% had seen ads for 10 or more products. 3.5% mentioned advertising as a contributing factor to seeing their doctor and 8.8% asked

specifically for advertised drugs. Although DTCA would seem to have a limited impact on Vancouver patients' behaviour the effects of having DTCA in Canadian media may produce a more significant change. The patients in Sacramento who participated in this project were definitely more influenced by DTCA. Limitations of this study have already been discussed.

81. A 2001 survey of 79 key Canadian informants (response rate 76%) from government, the pharmaceutical and advertising industries, private insurers, health professional groups, consumer groups and patient groups (Mintzes et al. 2005) produced results related to this issue. This study, by Mintzes and colleagues, entitled "*Introduction of Direct-To-Consumer Advertising of Prescription Drugs in Canada: An Opinion Survey on Regulatory Policy"* in *Research in Social and Administrative Pharmacy*, 2005 is attached as Exhibit 6 to this affidavit. These people were asked their opinions on questions about DTCA such as its effects on drug and health care use. "Opinions were highly polarized on the effects of DTCA on drug and health care use. Advertising and pharmaceutical industry respondents were generally positive, public sector, health professional and consumer groups generally negative." No one from the advertising industry thought that DTCA worsened patients' understanding of drug therapy and disease risks and only 20% of pharmaceutical industry respondents felt that way, but for consumer, patient and health professional groups the range was from 64% to 80%.

82. Besides the general cautions about surveys discussed above, an additional caveat applies to the overall results of the key informant survey. Since DTCA was (and is) not legal in Canada at the time, the respondents had no concrete knowledge to base their opinions on; at best they could have tried to extrapolate from the American experience.

83. One final Canadian study was a telephone survey of 165 members of the public in one city (Maddox and Katsanis 1997). The interviewees were presented with one of two hypothetical situations whereby they received information about a new “breakthrough” drug for colds either from their family doctor or through advertising. People who received the information from a doctor were much more likely to use the drug in the future than those who heard about the drug through advertising.

84. As part of their report on DTCA to the Minister of Health of New Zealand, Toop et al also commissioned a survey of the New Zealand general public on DTCA. The report is attached as Exhibit 7 to this affidavit. In total, 500 interviews were carried out leading to a margin of error of ± 4.4%.

- 52% felt that the accuracy and reliability of information in TV ads was somewhat or very untrustworthy with only 7% saying that it was somewhat or very trustworthy;
- 42% strongly or somewhat agreed that DTCA raises awareness of illnesses that people might not otherwise realize they have versus 18% who somewhat or strongly disagreed. A similar number strongly or somewhat agreed that patients are likely to seek treatment more quickly if they have seen an ad for a prescription-only medicine while 25% somewhat or strongly disagreed;
- 59% somewhat or strongly disagreed that drug company advertising provides unbiased and comprehensive information;

- 13% said that an ad had prompted them to ask for a prescription only medicine and 62% received the medication that they asked for with an additional 17% receiving another product.

85. Finally, Toop et al (2003) cite a British survey done by the Consumers Association of 1818 adults. The results of this survey are broadly in line with the one from New Zealand:

- 62% of people believe that drug company advertising would not give people information about possible side effects;
- 59% of people believe that drug company advertising would try and convince people that they have illnesses they do not really have;
- 60% of people believe that advertising of prescription-only medicines would raise awareness of illnesses that people might not otherwise realise they had;
- 53% of people believe that patients would seek treatment more quickly if they had seen an advert for a prescription-only medicine;
- 25% of people believe that drug company advertising would provide unbiased and comprehensive information about treatments, including non-drug treatments and competing brands.

86. Mintzes has summarized much of the U.S. literature on this topic (Mintzes 2001):

- Between 23% and 29% of respondents in national surveys of random samples of the US population spoke to their doctor for the first time about a drug or condition in response to advertising;
- Between 6 and 9% directly requested a drug and 5-7% received it, or 80-84% of those who had requested drugs. In one case about 10% received a competitor instead of the drug they had requested, another 71% received the requested drug;
- 5-8% said that they were reminded to take their medicine or refill a prescription because of seeing an ad for the product they were taking.

87. Changes in compliance with medications as a result of DTCA have been claimed as one of its benefits. Between one-quarter and one-fifth of U.S. consumers said that they were more likely to take their medication as a result of

seeing DTC ads. More than 2/3 said the ads would have no affect on their behaviour (Mintzes 2006).

Summary and Opinion

88. Canadian and international studies show that patients are highly sceptical about the quality of information in DTCA. Only representatives of the advertising and pharmaceutical industries seem to think that there are few or no problems with the information content of DTCA. These are the groups that stand to gain financially from DTCA. The fact that 80% of people receive the drug that they request may on the surface seem as if patients get appropriate information from DTCA, however that would mean that patients are accurate in both self-diagnosis and treatment selection 80% of the time, a figure that doctors would be hard to match. In my opinion, it is more likely that doctors are giving patients what they want so as not to alienate them. There is no evidence that patients have confidence in DTCA or that it improves their knowledge.

b. Physician attitudes and behaviour

89. A 1993 Master's thesis sent a survey to 1500 Canadian doctors chosen on a random basis but the response rate was under 20% (Heesels 1993). Out of the respondents just over 15% supported DTCA with just under 75% being opposed. The low response rate makes it difficult to generalize the results of this survey to Canadian physicians in general, plus attitudes may have changed over the past dozen years.

90. Although this survey is old, its results are reflected in the current statement about DTCA by the Canadian Medical Association which represents about 80% of Canadian doctors. The CMA “support[s] the provision of objective, evidence-based, reliable plain-language information for the public about prescription drugs” but regards DTCA as “marketing [that] sends the message that a prescription drug is a ‘consumer good’ rather than a health care benefit.” As a consequence the CMA “oppose[s] direct-to-consumer prescription drug advertising in Canada”. Attached as Exhibit 8 is the CMA policy as it appears in the association’s website.

91. The New Zealand survey by Toop and colleagues of general practitioners in that country (referred to above and attached as Exhibit 7) indicates a generally negative view of DTCA and its effects (Toop et al. 2003):

- 90% of respondents stated they had had consultations specifically generated by DTCA;
- 79% of respondents reported patients frequently asked them for DTC advertised medicines;
- 74% of respondents felt that DTC advertising of lifestyle drugs encourages the medicalization of well populations;
- 69% of respondents felt they had been under pressure to prescribe advertised medications;
- 68% of respondents felt consultations generated by DTCA were often unnecessary;
- 16% of respondents felt that DTC ads have helped their patients get necessary medical care at an earlier stage;
- 13% of respondents felt DTCA improved compliance;
- 12% of respondents believed DTCA was a useful means of educating consumers about the risks and benefits of prescription medicines.

92. Time magazine carried out a 1998 survey of U.S. physicians but only received a 21% response rate leading to questions about how generalizable

the results are (Mintzes 2001). The results indicate an overall negative attitude about DTCA albeit with some contradictory responses:

- 61% saw it as providing consumers with needed information;
- 69% thought it created confusion about the difference between prescription and OTC drugs;
- 78% thought it would lead their patients to request unnecessary or incorrect medication;
- 74% thought that it increased pressure on doctors to prescribe in response to requests.

Summary and Opinion

93. Although there are a few measures that show a favourable attitude towards DTCA by doctors, the bulk of the survey evidence from Canada, New Zealand and the United States indicates a generally negative opinion. The Canadian Medical Association, which speaks for the large majority of Canadian doctors, is on record as opposing DTCA. If DTCA is introduced into Canada most doctors would be opposed to it.

c. Doctor-patient relationship

94. Mintzes questioned her key informants on the issue of the doctor-patient relationship (Exhibit 6). Thirty percent of all respondents felt that it improves communication, 50% that it worsens it, 7% that is has no effect and 13% did not comment.

> Most public sector respondents believed that DTCA led to less appropriate prescribing, but nearly half expressed no opinion… Many health professionals also failed to comment; if they did, they usually rated DTCA's effects to be negative. Pharmaceutical industry responses were mixed, but advertising industry respondents mainly believed that DTCA has a positive effect on both prescribing and drug use… Another question concerned the effects of DTCA on appropriateness of physician consultations. Eighty-nine percent of nonprofits consumer groups, and

> 62% of public sector and private payer respondents generally believed that DTCA would decrease appropriateness of physician consultations; other sectors had mixed opinions.

95. DTCA could lead to a deterioration in the doctor-patient relationship in a minority of cases if patients' responses in some surveys are believed. In a 1998 national U.S. survey 11% agreed completely and 17% agreed somewhat that they would switch doctors to get the medication they desired (US DTC TV ads work, web "useless" 1998). In a Food and Drug Administration survey in 2002, 9% said they would switch doctors under these circumstances (Aiken 2002).

96. In another U.S. survey a few years later where patients were asked for their responses if they were denied requested medication. 46% said they would feel disappointed; 25% indicated they would try to influence the physician to change their mind; 24% indicated they would seek the prescription elsewhere; and 15% indicated they would consider terminating their relationship with that physician. Attached as Exhibit 9 to this affidavit is a copy of the report of the survey results by Bell, Wilkes and Kravitz, entitled "*Advertisement-Induced Prescription Drug Requests Patients' Anticipated Reactions to a Physician Who Refuses*" in the *Journal of Family Practice*, June 1999.

97. In the New Zealand GP survey, only 28% of respondents felt that DTCA did not lead to difficulties in the doctor-patient relationship (Toop et al.

2003). Toop also cites an earlier New Zealand survey of GPs that found that 61% believed that DTCA created disharmony in the doctor-patient relationship.

98. A U.S. survey of family physicians found that 89% of 454 doctors did not feel that DTCA enhanced the doctor-patient relationship and 71% believed that doctors were “pressured to use medicines they might not ordinarily use” (Lipsky and Taylor 1997). Mintzes notes that the Lipsky and Taylor article “has been criticized in a report by the American Medical Association’s Board of Trustees as not being representative of all US primary care physicians because the population they sampled from were only active members of the American Academy of Family Physicians” (Mintzes 2001).

Summary and Opinion

99. A good doctor-patient relationship is essential for appropriate treatment. Doctors and patients need to trust one another so that they can share information and jointly develop a plan for how to deal with the patient’s medical problems. The feeling amongst doctors and others, except for the advertising and pharmaceutical industries, is that DTCA has a negative effect on the doctor-patient relationship. Furthermore, about a quarter of patients in the United States state that if they did not get the medication that they requested that they would go elsewhere to get a prescription for the product. In my opinion, overall, DTCA will cause a deterioration in the doctor-patient relationship and lead to poorer treatment for patients.

F. ALTERNATIVES TO COMPLETE PROHIBITION

100. If DTCA is not completely prohibited there are three possible methods for regulation:

a. Industry self-regulation
b. Regulation by independent bodies
c. Direct government regulation

101. In this part of my affidavit I will examine each of these methods.

a. Industry self-regulation

102. As Lexchin and Kawachi (Lexchin and Kawachi 1996) note there are two major drawbacks to government regulation - one financial, the other practical. Increasingly, fiscal pressures in almost all countries have prevented government agencies from effectively policing pharmaceutical promotion. Government regulatory agencies rarely have the resources to make it economically rational for individual firms *not* to cheat. The other major drawback to government regulation is a lack of necessary expertise compared to industry.

103. Voluntary self-regulation therefore seems an attractive option because, lacking government-industry adversariness, it is a more flexible and cost-effective option. Government regulators also reason that in a highly competitive industry, the desire of individual companies to prevent competitors from gaining an edge can be harnessed to serve the public interest through a regime of voluntary self-regulation run by a trade association. However, although

misleading advertising may to some degree inhibit competition, it is also far more often good for business.

104. In Canada, interactions between sales representatives and doctors, company policy regarding gifts and payments to doctors and company conduct of continuing medical education are all governed by the voluntary code adopted by members of Canada's Research-Based Pharmaceutical Companies (Rx&D) (Canada's Research-Based Pharmaceutical Companies 2006). In my view, the code suffers from a number of drawbacks. It relies on complaints of breaches before it takes action rather than proactively monitoring compliance, the majority of the members of the committee that administers the code come from the pharmaceutical industry, there is no formal mechanism for regular reviews of the code, the fines for non-compliance are relatively small, it does not contain any provisions to enhance drug safety such as requiring sales representatives to inform doctors about important new safety information and companies can avoid being governed by the code if they resign from Rx&D. Attached as Exhibit 10 to this affidavit is an article I wrote entitled "*Enforcement of codes governing pharmaceutical promotion: What happens when companies breach advertising guidelines?*" dealing with this issue and which appeared in the Canadian Medical Association Journal in February 1997.

b. Regulation by independent bodies

105. Besides the United States, New Zealand is the only other country that currently allows DTCA. Industry practices there are regulated by a Code of Therapeutic Advertising which is administered by the Advertising Standards Complaints Board (ASCB), a body appointed by the Advertising Standards Authority (ASA), an advertising industry body. Coney (Coney 2002) gave an example of what happened when her organization, Women's Health Action Trust (WHAT), complained about a DTC advertisement.

106. Although this complaint was ultimately upheld, it took from June 1999, when it was initially lodged, until December 1999 for WHAT to be told that the complaint was successful. During this period WHAT was required to respond to several requests by the ASCB for more information, sign a waiver that it gave up any right "to take or continue any proceedings against the advertiser, publisher or broadcaster concerned," and adhere to a requirement not to make the result public before the ASA did. In addition to these onerous requirements on the part of complainants, Coney points out that the ASCB has limited powers. Its decisions are not binding or enforceable. The current executive director of the ASA says that it prefers voluntary compliance and an educational approach. Attached as Exhibit 11 is a copy of Coney's article entitled "*Direct to Consumer Advertising of Prescription Pharmaceuticals: A Consumer Perspective from New Zealand*" which was published in the *Journal of Public Policy & Marketing* in the Fall 2002 edition.

107. In Canada print advertisements directed at doctors are pre-screened before publication by the Pharmaceutical Advertising Advisory Board (PAAB) which applies the standards set out in its Code of Advertising Acceptance (Pharmaceutical Advertising Advisory Board 2006). Although PAAB is independent of the pharmaceutical industry the majority of members on its board come from organizations that benefit financially, either directly or indirectly, from advertising (Advertising Standards Canada, Association of Medical Advertising Agencies, Canadian Association of Medical Publishers, Canadian Generic Pharmaceutical Association, NDMAC (manufacturers of self-care products), Canada's Research-Based Pharmaceutical Companies). PAAB has no authority to levy financial penalties on companies that breach its code and has only rarely ordered companies to run corrective advertisements. Like the Rx&D, PAAB has no plan for regular review of its code. Its code allows companies to separate the detailed prescribing information from the main part of the ad, safety information can appear in type that is significantly smaller than that used to describe the benefits of the medication, and the generic name of the drug can be as small as 8 point on 9 point.

108. Problems with regulation by independent bodies are also apparent in looking at ads for nonprescription products that appear in Canadian magazines. Authority for ensuring that these ads conform to the rules set out by Health Canada has been delegated to Advertising Standards Canada. The Affidavit filed in support of the motion by Canwest Mediaworks Inc. contains a number of examples of ads for nonprescription drugs. One claims that women

who used Everslim ™ lost 3.5 times more weight than women who used dieting and exercise alone. However, there is no information about whether this weight loss was maintained after the women stopped using the medication. No safety information is mentioned in the ad.

109. Another ad for CoricdinHBP ™ claims to be beneficial for cough from colds and flu. However, a systematic review of medications for cough could find no evidence that any medication is effective (Schroeder and Fahey 2002).

110. A third ad for a homeopathic remedy called Oscillococcinum ™ maintains that it is effective for reducing the duration and severity of flu but has no side effects and no interactions with other medications. Any product with an active ingredient will have side effects or interactions in at least some patients. If this statement about Oscillococcinum ™ is correct then it could not have any active ingredient and could not be beneficial in the treatment of the flu.

c. Direct government regulation

111. Amendments passed in 1962 to the US *Food, Drug and Cosmetic Act* gave the FDA jurisdiction over prescription drug promotional campaigns and materials. The FDA has defined its authority to cover any material issued by or sponsored by a drug manufacturer that falls within the legal definitions of labelling or advertising (Kessler and Pines 1990).

112. However, the FDA is beset with limitations that undermine its ability to effectively control promotion. As a federal agency the FDA is chronically underfunded (Slater 2005) with the consequence that in the past, although the "vast majority" of promotional material submitted to the FDA's division of drug advertising and labelling were considered "false and/or misleading," the FDA was able to take action in only 5% of cases because of lack of resources (FDA's drug promotion problems 1989). These limitations were highlighted in a 1992 review of 109 journal advertisements. These were evaluated using criteria based on FDA guidelines. Overall, independent expert reviewers would not have recommended publication of 28% of the advertisements and would have required major revisions in 34% of them (Wilkes, Doblin, and Shapiro 1992).

113. Although the FDA does not review ads before they are disseminated, manufacturers are obligated under the US *Food, Drug and Cosmetic Act* to submit copies of all ads to the FDA at the same time as they are first used commercially. The Division of Drug Marketing, Advertising and Communications (DDMAC), the arm of the FDA that regulates promotion, continues to be overwhelmed by the volume of material it has to deal with. In fiscal 2002, DDMAC had 39 full-time-equivalent positions to review approximately 34,000 pieces of promotional material (General Accounting Office 2002).

114. The shortage of personnel is best illustrated by the case of direct-to-consumer advertising (DTCA). In 1997, the FDA loosened the regulations

around broadcast DTCA by removing the requirement for companies to provide all of the safety information on screen with the advertisement. Instead, companies thenceforth needed only to mention major side effects and contraindications in audio or visual form and state where consumers may obtain additional information. As a consequence the amount spent on DTCA rose from US $1.07 billion in 1997 to US $3.24 billion in 2003 (IMS Health 2005). But as of June 2002 DDMAC had only five staff dedicated to reviewing DTCA material which included 248 television ads and an unknown but certainly large number of print ads (General Accounting Office 2002).

115. Along with inadequate resources to review DTCA, there was also a marked change in the FDA's willingness to confront companies guilty of promotional violations. When the FDA identifies an advertisement that is noncompliant with its regulations, it sends a letter asking that the company cease disseminating the advertisement. In the late 1990s the FDA was sending out between 100 and 150 such letters a year, but that number started to decline dramatically in 2000 such that by 2003 only 25 letters were sent (Food and Drug Administration 2005). Moreover, there was an increasing delay in sending out those few letters that were issued. Prior to 2002, regulatory letters were typically issued within one month of the FDA receiving the ads but by 2003 the average delay was 177 days (United States House of Representatives Committee on Government Reform - Minority Staff Special Investigations Division 2004).

Summary and Opinion

116. None of the three methods used to regulate promotion – industry self-regulation, regulation by independent agencies or government regulation - are well enough resourced and independent enough to be able to adequately control promotion. In my opinion, attempts to regulate DTCA will not be successful based on experience with promotion of prescription drugs to physicians and the promotion of nonprescription drugs to consumers in Canada and the New Zealand and U.S. experiences with DTCA. It is my opinion that since regulation will not work a complete ban on DTCA should be maintained.

AFFIRMED before me at the City of Toronto, in the Municipality of Metropolitan Toronto, the 30th day of June, 2006.

Commissioner for Taking Affidavits*)*

JOEL LEXCHIN

05-CV-303001PD2

CANWEST MEDIAWORKS INC. AND ATTORNEY GENERAL OF CANADA

Applicant Respondent

ONTARIO
SUPERIOR COURT OF JUSTICE

Proceeding Commenced at Toronto

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