



# A Lethal Guardian

## The Canadian Government's Ban on Prescription Drugs

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Executive summary	/	1
History of government control over medicines in Canada	/	3
The international context	/	7
Drug loss and drug lag	/	10
Slowness does not equal safety—theory	/	18
Slowness does not equal safety—evidence	/	23
Losing the benefits of new medicines	/	32
Conclusions	/	37
Options for reform	/	38
Notes	/	41
Glossary	/	42
References	/	43
About the author & Acknowledgments	/	52
Disclosure	/	53
About this publication	/	54
<a href="#">How to use the interactive features in this document</a>	>	
About The Fraser Institute	/	55

## Executive summary

When any new drug is invented and ready for distribution in Canada, the Canadian government responds by enforcing an automatic ban on its use. This ban is removed for patients who need the drug immediately only under extraordinary circumstances. The general ban is only lifted after the manufacturer has paid a user fee and waited for Health Canada to undertake a lengthy review to certify the safety and efficacy of the medicine. This ban is harmful to Canadians' health and is implicated in the deaths of hundreds of Canadians annually. Although we cannot estimate the precise number of fatalities due to this untimely lack of new medicines, international evidence going back three decades supports the conclusion that any decrease in negative health outcomes resulting from avoiding the harmful side effects of new medicines is off-set many times over by the lost positive outcomes that would have occurred had the government allowed patients and health professionals to use new drugs sooner.

The time it takes Health Canada to lift its ban on new drugs is very long and, in fact, is increasing as time goes on. In 2002, the median time to remove this ban in Canada was two years. Yet, in 1997, it took just over 16 months. Therefore, the time to remove the prohibition has lengthened by 50% over the five-year period measured.

Although other developed countries have similar regulatory burdens, they take much less time to lift their bans on new medicines. In 2001, the Canadian government took eight months longer, at the median, than the United States to lift its prohibitions. During the three years from 1999 through 2001, Sweden lifted its bans seven months faster than Canada did, while the United Kingdom acted almost one-half year faster and Australia acted three months faster.

The United States performs better than Canada because it has many more resources available to review new medicines. It is not possible that Canada will be able to increase resources to a similar level. However, many smaller countries do a better job of reviewing new medicines with fewer resources than Canada. Canada's pharmaceutical regulatory productivity, as defined below, is 38% that of Sweden, and about half that of Australia or the United Kingdom.

Countries in the European Union have implemented a policy of regulatory competition, where a central regulator and national regulators compete for user fees that they charge manufacturers to lift their bans on new drugs. When one regulator has lifted its ban on a new medicine, all countries must generally reciprocate by lifting their bans. This competition has improved the productivity of regulators in the European Union.

Therefore, Parliament should amend the Food and Drug Act to allow Canadians to use new medicines once a regulator in a comparable jurisdiction, such as the United States, European Union, or Australia, has removed its prohibition. Health

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Canada would retain the right to compel manufacturers to label their medicines with the warning that Health Canada had not approved the safety or efficacy of the medicine. If Health Canada nevertheless wants to review the drug's safety or efficacy, it will be able to do so, using general government revenue. If the manufacturer wants Health Canada to review the medicine, with a view to removing its warning label, it would pay a user fee to have Health Canada review it.

The amended Act would require the Health Minister to make annual reports to Parliament containing information about the new drugs allowed in Canada due to this reciprocity, as well as the application and removal of warning labels by Health Canada, the number of prescriptions written as a result of these actions, as well as reported negative and positive consequences to Canadian patients' health associated with the faster use of new drugs.

After a period of five years, Parliament would review how Canadians have responded to the faster availability of new medicines due to these amendments, and introduce further regulatory reform based on that information. By giving Canadians the choice whether to adhere to Health Canada's recommendations or not, the government will be able to reform the regulations further to serve our needs.

## History of government control over medicines in Canada

The Canadian government has not always prevented patients from getting the medicines that they want by automatically banning therapeutic drugs. This increase in the state's power over individuals' choice really took place in the second half of the twentieth century. Nevertheless, Parliament had passed (and repealed or amended) a number of Acts relevant to drugs between 1874 and 1890. These laws authorized the Inland Revenue (predecessor of the Canada Customs and Revenue Agency) to test samples of food, drink, drugs, and fertilizer. The Adulteration Act of 1884 recognized the American and British Pharmacopœiæ as defining the standards and limits of variability of drugs and established a laboratory in Ottawa. One year later, a new Adulteration Act gave the Inland Revenue a mandate to publish bulletins informing the public about products in those four categories that had been adulterated by unscrupulous persons. Parliament later amended the law to provide for setting standards by Order in Council rather than legislation. That is, it gave the government the ability to set standards without coming back to Parliament for approval. In 1918 and 1919, the government transferred administration of the Act from Customs and Inland Revenue, first to Trade and Commerce and, finally, to the Department of Health. [Curran, 1953: 142–53; Goyer, 1986: 6–11]

### 1920—Food and Drug Act

Parliament passed the first Food and Drug Act in 1920. This Act introduced the offence of “misbranding” (a term borrowed from US legislation of 1906), and authorized the government to change the law through “delegated legislation” of the Governor in Council (that is, effectively, cabinet). In 1927, the Act was amended to require licensing for places that prepared products of animal origins, vaccines, serums, and so on. (Such products are what we now generally call “biologicals” and are still licensed by a different office within the department than that responsible for medicines of synthesized molecules. Today, biologicals include products of recombinant DNA). The amendments also gave the government the power to regulate and inspect places of manufacture. [Curran, 1953: 153–54; Goyer, 1986: 6–11; Proud, 2004]

An amendment of 1934 was the first direct interference in the right of manufacturers and patients to communicate with each other: it prohibited the advertising to consumers of drugs listed on a schedule of serious illnesses; a prohibition that still exists today. An amendment of 1941 increased the power of physicians over patients and manufacturers by imposing the requirement of a prescription for some drugs. [Curran, 1953: 154; Goyer, 1986: 6–11]

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## 1951—Notice of Compliance

Regulations introduced in 1951 greatly increased the state's power by imposing an automatic ban on new medicines. These regulations prevented manufacturers from selling, and patients from using, medicines until the manufacturer had submitted data on the safety of a new drug. Upon receipt of a complete submission, the government would then issue a Notice of Compliance (NOC) lifting the ban. The NOC allows the manufacturer of a prescription drug to distribute the medicine to patients through the laws and regulations governing prescribing and dispensing in each province and is still the document the government issues to remove the ban.

This new requirement was similar to the US requirement that came into effect in 1938. Thus, for 13 years, Canada actually allowed manufacturers, physicians, and patients more freedom to transact than the United States did. [Curran, 1953: 180] The regulations of 1951 also increased government oversight of clinical trials by compelling manufacturers to inform the relevant division within the department before distributing a prospective drug for clinical trial. A new Act in 1953 prohibited manufacturers from giving samples of drugs to the general public and authorized the government to stop the sale of a drug that showed evidence of hazards of use, that is, was unsafe. [Goyer, 1986: 6–11; Proud, 2004]

## 1964—the Hall Commission and the efficacy of drugs

However, reports from that period indicate that the government's lifting the ban by issuing a NOC was reactive rather than active: a matter of receiving the paperwork. Government control of Canadian health care increased drastically as a result of the recommendations of the Hall Commission, which reported in 1964, and was the impetus towards what we now call Medicare. According to the Commission, the Food and Drugs Act of 1953, as amended in 1960/1961, “gives no authority for the approval of anything or any action. Any drug or medical device not violating the Act or Regulations may be sold.” [Royal Commission on Health Services, 1964: 16] Nor did the research-based, brand-name drug makers (or, as they referred to themselves at the time, “ethical drug makers”), think that it was the government's job to take the initiative in approving or allowing a drug. In 1962, the Chairman of the Medical Section of the Canadian Pharmaceutical Manufacturers Association wrote: “It is not within the function of the Food and Drug Directorate to guarantee the quality of drugs sold in Canada, this assurance being provided by the trademark adopted by the manufacturer.” [Parker, 1962] Furthermore, the Act required the manufacturer to submit data on safety but not on efficacy, which the law allowed the interested parties (manufacturers, physicians, and patients) to decide amongst themselves.

In summary, laws and regulations until this point generally presumed a new medicine to be innocent until proven guilty, although the regulations of 1951 shifted the bias somewhat. However, the amendments of 1963 drastically changed the rules. Most importantly, the amendments required manufacturers to demonstrate the efficacy, as well as safety, of a new drug to the government before it would issue an NOC. This greatly increased manufacturers' burden of communication with the government, because it takes a lot more data from clinical trials to demonstrate efficacy than safety. The amendments authorized the government to suspend an NOC, but also to suspend an Investigational New Drug Submission (INDS), that is, an application made before commencing clinical trials, and to inspect manufacturing plants. Regulations introduced in 1973 added a Drug Identification Number (DIN) to the NOC, and regulations from 1974 required an NOC for clinical trial protocols too. [Goyer, 1986: 6–11; Proud, 2004]

These amendments greatly increased the federal government's control over research and development, manufacturing, and distribution (while leaving all the risk in the hands of those who chose to invest in the drug-making enterprises). In summary, the bias changed to indict a new drug as guilty until proven innocent.

## Regulation, slow approval, and user fees

As explained below, this increasing burden of regulation caused the approval process for new medicines to slow down to a degree unacceptable to patients or manufacturers. In an attempt at speeding things up, Health Canada introduced user fees to recover costs in 1995. This increased the department's revenue from a source other than Canadian taxpayers because manufacturers were levied the fees when they submitted new medicines for approval. However, this initiative has also proved a failure, especially in comparison to international standards.

In 2002, the federal government appeared to make improving approval times a priority and the Throne Speech committed the government to speeding up the regulatory process. [Proud, 2004] This commitment included increasing the regulatory budget. In 2000, Health Canada had spent \$50 million on approving drugs. The Canadian government's 2003 budget pledged \$190 million of increased funding for 2003 through 2008 to improve the timeliness of reviewing applications, of which it allocated \$31 million for the 2003/2004 fiscal year. [Lexchin, 2004; Lexchin and Mintzes, 2000]

Health Canada has responded with a "Therapeutic Access Strategy" to improve its regulatory processes. The department has stated that it will make available to the public information and documents that explain why drugs or medical devices are authorized or not and, as well, publish annual reports. [Health Canada, 2003; 2004] However, more details about the content and timing of these reports have not been

forthcoming. Canada has also signed agreements with the United States and Australia (another laggard, by international standards) to share information, with the goal of speeding up approvals. [Blouin, 2004]

## User Fees Act

Given the increase in user fees that government departments were charging for services that they required private parties to use, some in Parliament wanted more accountability and better performance from departments in return for the revenues that they were taking from the private sector. Therefore, Parliament passed the User Fees Act, which came into force in March 2004 and which the President of the Treasury Board must review in 2007. This Act regulates the relationship between a regulatory agency and its “client,” in this case, Health Canada and the drug makers who submit new medicines for approval. For regulatory agencies levying user fees, the User Fees Act causes the agency to set standards of performance that are comparable to those of similar agencies in Canada’s trading partners. If a proposed user fee is higher than that charged by a regulator acting in a similar capacity in another country, the Minister must inform Parliament of the reasons for the difference and table a proposal justifying the user fee.

If a “client” complains that a user fee is too high, the law causes the creation of an independent advisory panel of three persons: one each from the regulatory agency and the private applicant, and a third to which both parties must agree. The panel reports to both of the parties but the law does not give it power of enforcement, that is, it cannot fix the user fee. However, the panel may award costs to one or both parties. If the complaint is vexatious or frivolous, it may charge all costs to the complainant.

Where the agency does not meet its targets for a fiscal year, and falls short by at least 10%, the user fee will be reduced for the next year by up to 50%. Parliament can resolve to approve a user fee and its reduction or not. Finally, the Minister must make an annual report to Parliament as to the user fees in effect.

Although the User Fee Act appears to increase Health Canada’s accountability, its sanctions do not appear to be very harsh. It is not clear that the Act actually requires Health Canada and other departments to improve their performance; it only formalizes how they set their fees and allows Parliament to intervene under certain circumstances.

## The international context

Canadian laws and regulations with respect to prescription drugs have largely followed those of the United States. Although the US Food, Drug, and Cosmetic Act required licensing of drugs for safety in 1938, while Canada did not do so until 1951, Canada's 1963 amendments swiftly followed similar changes in the United States. Because most of the research on the effects of increased government control over therapeutic drugs analyses US data, it is necessary to understand American legislation and regulations as well as Canada's. Furthermore, the policies of the European Union (EU) are similar to those in both Canada and the United States in most respects, but differ in several aspects that improve European regulatory agencies' performance in approving new medicines.

### The US Food, Drug, and Cosmetic Act of 1938

In the United States, the first law to require a manufacturer to get the government's approval before distributing a medicine was the Food, Drug, and Cosmetic Act of 1938. Its initial draft did not require such approval, merely granting the federal government policing powers (to prosecute after the fact), which it had actually enjoyed since 1906. However, a new drug with an untested solvent (diethylene glycol) killed over a hundred people within a few days while the bill was working through Congress. Therefore, Congress changed the bill to require drug-makers to submit a New Drug Application (NDA) for approval by the Food and Drug Agency (FDA) before introducing a new medicine into interstate commerce. At that point, the NDA was required to demonstrate safety (but not effectiveness). However, if the FDA took no action within 60 days of the application, the agency was deemed to have approved the application.

[Miller, 2000: 12–13]

The 1938 Act and its predecessor (passed in 1906) were effective in authorizing the government to act against those who marketed adulterated and misbranded drugs. [Miller, 2000: 13] In 1962, however, the American government passed amendments that drastically increased the regulatory costs of medicines. The 1962 (Kefauver-Harris) amendments required affirmative, pre-market, approval: that is, the absence of response by the FDA no longer passively signaled its approval of the new medicine. Furthermore, the amendments required that manufacturers receive the FDA's approval before any human testing could occur, or advertisement or label be put before the public. The 1962 amendments also required that drug-makers demonstrate that a new medicine be effective as well as safe and gave the FDA authority to promulgate Good Manufacturing Practices (GMP); that is, instructions about how the medicines are



made in the factories. The 1962 amendments fundamentally changed pharmaceutical research through increasing the costs of regulation. Research output collapsed, as measured by the number of applications to begin clinical testing for new chemical entities (NCEs). [Miller, 2000: 14–15]

### **Thalidomide**

The 1962 amendments to the US Food, Drug, and Cosmetic Act had languished in Congress until the negative effects of thalidomide, a sedative prescribed to pregnant women, became apparent. In 1958, Merrell, an American company, had licensed thalidomide from its German manufacturer for distribution in the United States. Merrell submitted an NDA to the FDA in November 1960. The FDA's examiner, Dr. Frances Kelsey, reported that Merrell had contacted the FDA 50 times in order to speed approval of the drug. However, Kelsey heard reports from Europe of the drug's causing nerve damage (to the pregnant women, not their fetuses) and accused the company of withholding information from her. Merrell responded by threatening to sue the FDA. Before the drug was approved in the United States, further bad news came from Europe, this time linking thalidomide to birth defects. This news increased public support for more regulation and added momentum to the amendments moving through Congress. [Daemmrich, 2004: 26, and references; Harris, 1992] Today, thalidomide is often held up as an example of why we need more testing before a government lets patients use a drug. However, it actually shows the limits of pre-market testing. After the birth defects were observed, subsequent trials conducted on the most commonly tested animal species, which were designed to replicate thalidomide's consequences, generally failed to produce the birth defects. [Gieringer, 1985: 193–94, and references]

The increased regulatory burden in the United States had the effect of increasing the time it took the US government to lift its ban on new medicines. Therefore, Congress passed the Prescription Drug User Fee Act (PDUFA) in 1992 (a few years before Canada introduced user fees), requiring it to be renewed every five years. The brand-name drug-makers strongly support PDUFA, associating the law with speedier approval times. [PhRMA, 2004: 15]

## **Drug approval in the European Union**

With the development of the European Union, manufacturers gained multiple avenues to having the ban on their medicines lifted. In general, manufacturers wishing to market drugs in Europe have a number of choices: they may either submit their drug to the European Union's central regulator or make a submission to one of the national regulators in the European Union. Approval from any one of these regulators can be used to nullify the ban on sales in other member states. Notable exceptions include

manufacturers of biotech products, who must submit their product to the central regulatory agency for approval. Also, in 2002 and 2003, the European Union decided to require medicines for cancer, AIDS, diabetes, and neuro-degenerative diseases to be approved centrally. [Ceccoli, 2004: 136–37]

The European Agency for the Evaluation of Medicinal Products (EMA), established in 1995 and headquartered in London, acts as the central regulator for the European Union with authority to license drugs throughout the European Union. The European Union has also amended procedures for mutual recognition (which had been introduced in 1983 but was initially optional for countries) whereby the EMA serves a quasi-judicial function: if a member does not accept another member's recognition, then the EMA can make a binding decision. However, if a manufacturer submits its drug application directly to EMA's Committee on the Propriety of Medicinal Products, which has two members from each member-state, it does not also have to submit to a national regulatory agency. The standard for review is that EMA's experts submit their recommendation to the European Commission within 210 days and the Commission makes its decision on approval within 90 days after that. [Miller, 2000: 38–39] The fact that drug-makers can seek approval through different regulatory routes has created competition for user fees among those regulatory agencies. [Abraham, 2002a] Furthermore, the EMA chooses reviewers from an external, multinational pool of qualified persons, whereas the American and Canadian regulatory agencies review new medicines "in house." [Miller, 2000: 38–39] The FDA has experimented, weakly, with third-party reviewers for medical devices, but not for drugs. [Campbell, 2000: 321–22]

What all three jurisdictions have in common is an increasing reliance on user fees from companies applying to have the bans removed from their medicines. Starting in the late 1980s, European countries such as the United Kingdom, Sweden, and Germany restructured their regulators and increased reliance on funding from user fees rather than general taxation. [Abraham, 2002a] As noted above, the United States and Canada did the same starting in 1992 and 1995. Of all these agencies, the US FDA is the most expensive for the applicant. As of 2001, the FDA charged manufacturers approximately US\$250,000 for review whereas the other jurisdictions charged between US\$90,000 and US\$100,000. [Rawson, 2002: 76]

## Drug loss and drug lag

The most obvious effect of the government banning prescription drugs for a period is that it takes longer for patients to get them. Scholarly research on the effects of increased government intervention goes back to the 1970s in the United States but only recently has it appeared in Canada. Researchers have coined two terms to describe the consequences of the increased regulatory burden: drug loss and drug lag.

The requirement that a manufacturer demonstrate efficacy in addition to safety to the government is very expensive. Clinical trials for drug effectiveness are costly, even if only testing a new drug against a placebo, because they are conducted on sick patients, whereas testing for safety is done on healthy subjects (who are easier to enroll). It now takes 60 or more clinical trials covering almost six-thousand subjects to meet the FDA's requirements. [Becker, 2002]

### Research on drug loss in the United States

Drug loss is more difficult to measure but may be more detrimental to patients' well being in the long term. It refers to the fact that the increased burden of regulatory compliance reduces the productivity of research and development (R&D). Every dollar invested in R&D produces less benefit for patients because more of that capital is spent to satisfy bureaucratic requirements, which not all patients value. Most of the research on drug loss has considered the effects of the 1962 (Kefauver-Harris) amendments in the United States.

A staff report for a US government inquiry on the effect of the amendments determined that manufacturers launched an average annual 42 new chemical entities (NCEs) during the period from 1950 to 1962 but only 14 during the period from 1963 to 1975. [Stone, 1977] A decade after the amendments, Professor Sam Peltzman analyzed their effect. He determined that the number of new chemical entities (NCEs) introduced annually from 1963 to 1970 was only 39% of the number introduced annually from 1951 to 1962. Primarily because his analysis informed him that patients' demand for new medicine had not changed over the period, he attributed all of this drug loss to the increased regulatory burden of the 1962 amendments and determined that the drugs lost would not have been less effective than those that survived. That is, the regulations caused a real loss of choice for patients. [Peltzman, 1973; 1974]

The only other economic analysis of the 1962 amendments in the 1970s was an unpublished Ph.D. thesis (by James Jondrow, cited here from secondary sources). This thesis challenged Peltzman by arguing that the 1962 amendments killed ineffective, not effective, drugs. [Gieringer, 1985: 182, and references] However, the FDA's own

calculations showed “important” NCE’s dropping from 6.23 to 3.73 over the two periods. [Stone, 1977: 9] According to report in 1977 of the government inquiry’s staff economist, although Jondrow and others have criticized Peltzman, none have offered satisfactory, competing explanations for the drug loss. [Stone, 1977: 25] Furthermore, Peltzman’s critics only challenge his argument that all the drug loss was due to the 1962 amendments. None deny that the amendments caused some of the drug loss.

The 1980s saw new research, more specifically on the effects of the 1962 amendments on the productivity of R&D. Professors Henry Grabowski and John Vernon criticized Peltzman’s estimates because he employed the concept of consumer surplus to estimate the demand for medicines, which they considered inappropriate. They argued that it is difficult to generate a meaningful, classical aggregate-demand function because patients do not select the prescription drugs they use. Nevertheless, using different methods and data, Grabowski and Vernon found that drug-makers faced a serious decline in R&D productivity from 1962 to 1975, as measured by the ratio of the number of patents to the number of R&D employees. The reduction was over one half. [Grabowski and Vernon, 1981: 8–9; 1983]

Perhaps a more subtle effect of the regulations was the reduction in competition caused by the high cost of regulatory compliance. Professor Lacy Thomas found that the 1962 amendments had a devastating impact on small pharmaceutical firms (and, of course, their ability to conduct R&D), thus entrenching larger firms. However, she also found that innovation did not decline for larger firms, which differs from other studies. [Thomas, 1990] We still see an echo of this today, in that the brand-name pharmaceutical industry continues to consolidate. This consequence of the 1962 amendments may explain why today’s brand-name drug-makers do not lobby for drastic reform, such as repeal of the 1962 amendments or the abolition of the FDA and other countries’ regulators, which impose such large costs upon them. (Rather, they support hefty user fees as long as the FDA approves drugs within a certain period.) The excessive regulation favours larger firms by imposing proportionately greater costs on smaller companies than on larger ones; therefore, the large ones are more likely to favour it. (Furthermore, the fate of surviving smaller companies hinge upon the favour of these regulatory bureaucracies; therefore it would not serve them, acting individually, to vigorously attack the FDA and its counterparts in other countries. [Miller, 2000: 5]

Another facet of the problem of drug loss is that the costs of regulatory compliance are fairly fixed, no matter the population or incomes of the relevant patients. This means that manufacturers will necessarily pull back from R&D on diseases disproportionately affecting fewer patients and patients with lower incomes. Thus, “minorities” stand to suffer more from drug loss. [Tabarrok, 2000: 32] (One approach to rectifying this in the United States is the Orphan Drug Act, which gives greater protection of intellectual property to medicines targeted at smaller groups.

Perhaps because there have been great therapeutic advances in new prescription drugs and perhaps because the research-based pharmaceutical industry, patients, doctors, and other interested parties have become used to the status quo, little research on the problem of drug loss has been done recently. [1] To paraphrase the late US President Kennedy, it is easier to look at things as they are and ask: "Why?", than it is to look at things as they could have been and ask: "Why not?"

### ***Drug loss in Canada***

It is unlikely that Canadian regulatory policy can significantly change the problem of drug loss because Canada comprises a tiny share of the world market for prescription medicines. For the 12 months through May 2004, Canadian sales were US\$9.3 billion, about 2% of the world market, whereas US sales were US\$177.1 billion. [IMS Health, 2004] When developing global R&D plans, it is unlikely that either investors or managers in global, research-based drug-makers take Canadian policy into account. However, the regulatory climate in the United States certainly has had an impact on global R&D and its output.

## **Drug lag**

The fact that US policy has negatively affected the output of innovative prescription drugs does not excuse Canada's failure to address the second problem, drug lag. Indeed, if the global output of innovative medicines is less than it could be, due to American regulations, it makes it more imperative that the Canadian government remove obstacles preventing Canadians from getting those medicines that are invented as quickly as they would prefer.

Drug lag is often defined across countries, measuring how much longer it takes for one country to remove its ban on a new medicine compared to another country that does so more quickly. American observers coined this term for the increasing lag in time to approval in the United States until the 1990s, compared to time to approval in European nations, especially the United Kingdom. The 1962 (Kefauver-Harris) amendments led to a period when the United States seriously lagged other developed countries in the introduction of new medicines. The 1962 amendments gave the FDA a huge increase in authority over both lifting the ban on new medicines and defining the criteria for conducting clinical trials. In the 1970s, a number of analysts examined the United State's growing drug lag when compared to other countries, mostly in Europe, though it lagged even Canada for some periods. Nevertheless, the FDA continued to assert that there was no drug lag. [Ceccoli, 2004: 75–94, and references]

The evidence showed, however, that average time for review in the United States rose from under two years to over three years between 1962 and 1989, while

average testing time rose from three years to between six and seven years. [Ward, 1992] The publication of studies that demonstrated that the United States lagged Europe in reviewing new drugs helped to motivate improvement in the United States. [Hansen, 2000: 281]

Furthermore, other, more dramatic, events also focused public attention on the FDA's role in denying patients the ability to get medicines they needed. One impetus for reform of the FDA was the attention drawn to the bottleneck holding up AIDS drugs by gay activists. In October 1988, a large rally took place outside FDA headquarters. Gay activists accused the FDA of causing deaths and demanded that patients have input into regulatory decision-making. One scholar has argued that gay activists were more successful than other patients' groups in seizing the initiative in pushing back the government because they had already organized a movement to achieve political and cultural change in the United States and were better prepared to challenge the state when the virus hit their community. [Daemmrich, 2004: 30–31]

An increase in staffing at the FDA's division responsible for approving new drugs and consequent reduction in approval times started in 1986, a few years before PDUFA was introduced in 1992. [Carpenter, et al., 2003: 621–22] However, according to a number of measurements, PDUFA is associated with dramatic improvements in the FDA's approval times, both year-over-year and with respect to other countries. According to an academic analysis, mean approval times for all drugs approved between 1984 and 2001 dropped from more than 30 months (2.5 years) before PDUFA's passage to 16.8 months (1.4 years) subsequently. [Tufts CSDD, 2002]

According to the US government's auditor, median approval time dropped from 27 months in 1993 to 14 months in 2001. [US GAO, 2002: 3] According to the brand-name drug-makers' trade association, PDUFA has cut average (rather than median) review time from 30.2 months in 1991 to 16.9 months in 2003. Furthermore, the FDA approved 21 new drugs in 16.9 months in 2003, compared to 17 drugs in 17.8 months in 2002. Not surprisingly, research-based drug-makers generally support user fees and lobby for the continuation of PDUFA, which is renewed every five years. Companies expect to pay \$1.2 billion in user fees to the FDA between 2003 and 2007. [PhRMA, 2004] (However, although PDUFA has allowed the FDA to hire more people to assess applications, it is not clear that it has made the agency more productive. [Carpenter, et al., 2003] That is, the agency may not be giving "more bang for the buck," even though it is giving more bangs for more bucks.)

Furthermore, the improvement in the FDA's performance is also apparent in international comparisons. Indeed, drug lag is no longer an issue for the United States. Since 1996, the United States has become the first market for over half of the new prescription drugs that are approved in that country. [Tufts CSDD, 2002]

### Drug lag in Canada

On the other hand, Canada has not only underperformed the United States but has failed to address the problem satisfactorily as the United States has improved. For 1981 through 1984, the Canadian mean review time for a New Drug Submission (NDS) for a New Chemical Entity (NCE) was 24.6 months, whereas the United Kingdom took 5.8 months and the United States took 12.3 months for new drugs with major or modest therapeutic advances and 19.5 months for those with minor advances. [Goyer 1986: 37]

Between 1985 and 1992, the Canadian government sponsored a number of reviews of the time it took Canada to approve new medicines compared to other countries, finding that Canada took significantly longer. However, the last report was published in 1992. [Rawson and Kaitin, 2003: 1403, and references]

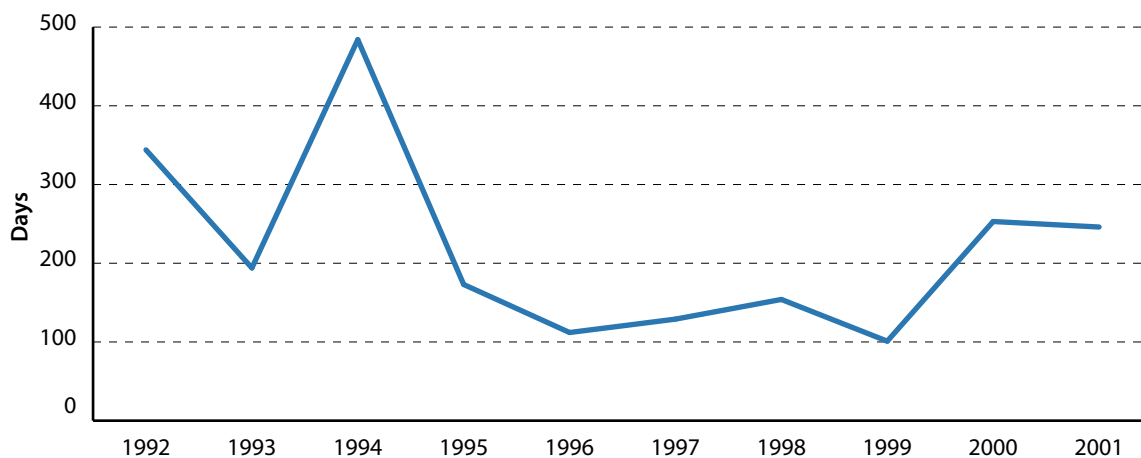
Although Canada has speeded up its approval since the late 1980s, other countries have done so too, so Canada still faces a relative drug lag. [Rawson and Kaitin, 2003: 1404] During the 10 years from 1992 to 2001, Health Canada lifted its ban on significantly fewer medicines than did the FDA: 295 versus 337 (for which the dates to approval were available). However, despite approving fewer drugs, Health Canada took 6.3 months (192 days) longer than the FDA to approve them, at the median. [Rawson and Kaitin, 2003: 1404] Both the FDA and Health Canada have been improving their times to approval [Table 1] but Health Canada seems to have stalled in the last few years. Because the FDA continues to improve, Canada's lag (which was steady in the late 1990s) has been increasing since 1999. [Figure 1] Furthermore, Canada's absolute performance from year to year, independent of what the FDA has achieved, has been getting worse since 1997, with the median time to lifting bans on medicines increasing by almost one half by 2001.

**Table 1: Median drug approval times in Canada and the United States, 1992–2001, by year of approval**

	Canada (days)	United States (days)	Difference (days)	Difference (months)
1992	1057	713	344	11.3
1993	862	668	194	6.4
1994	876	392	484	15.9
1995	628	455	173	5.7
1996	567	455	112	3.7
1997	490	361	129	4.2
1998	518	364	154	5.1
1999	577	476	101	3.3
2000	646	393	253	8.3
2001	704	458	246	8.1

Source: Rawson and Kaitin 2003: 1404; author's calculations

**Figure 1: Difference between median drug approval times in Canada and those in the United States, 1992–2001**



More recent figures, from surveys compiled and published by the research-based drug-makers' trade associations in both countries show the trend continuing. Canada's performance is deteriorating and that of the United States is continuing to improve. In 2002, the Canadian median time-to-approval for 13 new drugs was 24.0 months (729 days). [Rx&D, 2003: 5] For 2003, Rx&D reported average, rather than median, time-to-approval, which showed an improvement to 618 days from 682 in 2002. However, Health Canada also approved fewer new drugs in 2003 than 2002: 11 rather than 13. [Rx&D, 2004: 1; Rx&D, 2002: 5] With this in mind, it is questionable whether this was really an improvement. If Health Canada had the same resources in both years, it should have been able to approve 11 drugs in 577 days ( $\frac{11}{13}$  of 682). The US trade association also reports the average rather than the median. The FDA's approval time improved to 16.9 months in 2003 versus 17.8 months in 2002. [PhRMA, 2004: 1]

The situation for Canadian patients is made worse by the fact that drug makers sometimes submit their medicines for approval earlier in the United States than in Canada, thereby making the actual delay for Canadian patients worse than the simple day count indicates. Of 78 drugs approved in Canada from 1999 to 2001, 29% had been submitted six months earlier or more in the United States, and 19% more than one year earlier. [Rawson, 2003: 1242]

Furthermore, the United Kingdom and Sweden perform better than Canada. (Note that drug makers can use approval in one country to achieve mutual recognition in other states of the European Union; therefore, these figures likely approximate those for other EU countries as well.) Australia also performs somewhat better than Canada. For the three years from 1999 to 2001, Table 2 shows the median time to approval for new drugs in five countries.



**Table 2: Time to approval for new drugs in five countries, 1999–2001**

	Number of new drugs approved over 3 years	Median time to approval (days)	Faster than Canada (months)
Canada	78	645	N/A
Australia	89	551	3.1
Sweden	89	431	7.0
United Kingdom	71	479	5.5
United States	85	371	9.0

Source: [Rawson 2003: 1235](#); author's calculations.

Canada approved fewer drugs than either Australia or Sweden but took several months longer to do so. Furthermore, although Canada approved a handful more drugs than the United Kingdom, it took almost half a year longer to do so. Nor is Canada's underperformance relative to these other countries, especially Sweden and the United Kingdom, a function of lack of resources applied to the issue. Professor Nigel S.B. Rawson, who analyzed the above data, also looked at the number of personnel (full-time equivalent) employed in approving new drugs at each national regulatory agency. [Table 3](#) shows that Canada is second only to the United States in this count. Especially remarkable is the low head-count in the United Kingdom, a country with a population more than twice as large as Canada. Given the number of new drug applications in each country, we see that Canada has twice as many regulatory personnel approving new drugs as the other countries, aside from the United States. Though some may suggest that longer approval times in Canada could be symptomatic of a more thorough review process, this really cannot be. The FDA has about 10 times as many people working on new drug approvals as Health Canada does. Furthermore, the editors of the *Canadian Medical Association Journal* have complained that in the area of post-marketing surveillance (rather than initial drug approval), Health Canada lags the FDA in issuing warnings. [[CMAJ, 2001](#)]

**Table 3: Staff for drug approval and drug applications in five countries**

	New drug approval staff, full-time equivalent, 2000	Average annual number of applications for new active substances, 1999 through 2001	Full-time equivalent staff per application
Canada	159	26	6
Australia	76	30	3
Sweden	46	30	2
United Kingdom	60	24	3
United States	1,610	28	57

Source: [Rawson 2002: 75](#); [Rawson 2003: 1235](#); author's calculations (figures rounded to whole numbers).

Given these variables, we can calculate a simple productivity index of pharmaceutical regulation for these five countries, with Sweden as the most productive. **Table 4** shows this index as a function of the full-time equivalent staff per application and the median time to approval in the five countries. The first thing that jumps out is that the productivity of the United States is extremely low, despite its short time to approval: the FDA employs too many people and costs too much. In 2000, Health Canada spent CDN\$50 million on drug approvals, where the FDA spent CDN\$745 million. [Lexchin and Mintzes, 2000] During 2000 and 2001, the FDA charged manufacturers approximately US\$250,000 for review, whereas the other jurisdictions charged between US\$90,000 and US\$100,000. [Rawson, 2002: 76]

This really brings into question the approval that the FDA has earned from the research-based pharmaceutical industry for its recent performance. However, it may be that the industry has little interest in ridding itself of its primary regulator (as hypothesized above) or that it accepts that the regulatory state is too entrenched in the United States to be challenged. Furthermore, we should not take this productivity index too seriously. Given that the US FDA is the fastest regulator today, it is likely that other regulators free ride on the FDA's approval, simply waiting for the FDA to do its work and then waiting a while longer to see if anything untoward occurs after approval in the United States.

In any case, it is not the purpose of this paper to analyze the shortcomings of the FDA's drug approval process, but Health Canada's. Of the four smaller countries, Canada is obviously the laggard in productivity, getting less for more than Australia, Sweden, or the United Kingdom. Canada's pharmaceutical regulatory output is 38% that of Sweden and about half that of Australia and the United Kingdom.

**Table 4: Productivity of new drug approvals for five countries, 1999–2001**

	Full-time equivalent staff per application	Median time to approval (days)	Productivity Index (27,800 * full-time equivalent staff per approval / time)
Canada	6	645	38
Australia	3	551	77
Sweden	2	431	100
United Kingdom	3	479	68
United States	57	371	2

Source: Rawson 2002: 75; Rawson 2003: 1235; author's calculations (figures rounded to whole numbers).

Note: Productivity Index is a function of 27,800 in order to normalize Sweden to 100.

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## Slowness does not equal safety—theory

We have seen that Health Canada takes significantly longer than other countries' regulatory bureaucracies to do the same job that the others do—recognize that the prescription drugs used by patients in Canada are safe and efficacious. However, if the effect of Health Canada's interference in the availability of new medicines in Canada is that Canadians enjoy safer and more effective prescription medicines, then the cost may be worth it. This has been the position of the government. According to a departmental publication: "If Health Canada's experts are not satisfied that a drug submitted for approval is safe or effective, they will not grant a marketing authorization. That's one reason why some drugs available in other countries may not be approved for sale in Canada." [Health Canada, 2001: 2] Both theory and evidence, however, contradict this position.

### Government policy reduces information available to consumers

Standard arguments in favour of regulation start from the position that individuals are poorly informed. This idea is well developed in neo-classical economic theory and includes counter-intuitive insights such as that people can remain poorly informed even if they think that they have fully and effectively searched for information. [Stiglitz, 2000; Higgs, 1994: 1–4] Common sense also tells us that people are not equally capable of learning about medicines that drug-makers want them to use. Because it is not easy for us to learn about the effects of medicines, most individuals will be greatly less informed than manufacturers of a given medicine. Given that it is costly for patients to inform themselves, manufacturers will not be motivated to communicate risks to them fully.

However, there is a difference between banning a medicine and improving the available information about it. [Higgs, 1994: 6] Canadian policy with respect to improving the quality of information about medicines is poor. The government bars patients from buying most drugs on their own (without a prescription), allows physicians to prescribe only from an approved list, and prevents drug companies from disseminating information that the government has not approved. Thus, government policy provides a disincentive for patients to become informed (by raising the cost of doing so) and thereby prevents information from disciplining the pharmaceutical market. [Ward, 1992] Because the government generally bars drug makers from communicating to (potential) patients in Canada, pharmaceutical companies cannot link their names effectively with their products in the layman's eye, which would increase the incentive to compete on safety for the sake of their reputation. Such competition exists in other markets. For example, Volvo and Fisher-Price® invest in identifying

their brands with safety in the automobile and toy markets. As with the government banning the use of new medicines, banning manufacturers' information about them does not guarantee that better information will fill the vacuum. We simply face a choice of low or zero levels of "unbiased" information versus high levels of "biased" information. [Tabarrok, 2000: 42 fn]

Furthermore, although the costs of bad choices in health care are high, the benefits of good choices are huge. Therefore, we would expect patients, their loved ones, and care-givers to invest much effort in learning about a possible therapy. Similarly, we would expect intermediaries to intervene to lower the costs to patients of obtaining high-quality information. There are other areas where individuals face poor information and serious consequences of their decisions but the government leaves them alone to decide. Despite poor information, individuals nevertheless know better because they largely face the consequences alone. Consider marriage, where choosing a partner is fraught with personal, financial, and physical risk yet the government generally lets adults decide for themselves. [Campbell, 2000: 328]

Although banning drugs, as the government currently does, might benefit some (e.g., patients who are absolutely unwilling or incapable of informing themselves adequately), patients overall would benefit even more if the ban were replaced by a warning label stating that the regulator considers the drug to be unsafe or ineffective. This is because informed patients could then use the drug while patients who were ignorant or more averse to risk would veer away from it. [Hanson, 2003: 2014] On the other hand, abolishing the ban does not create an equal and opposite effect: the government does not force any patient to use a drug that he would prefer not to take.

Certainly, studies of government-mandated warnings on items such as seatbelts, alcohol, and cigarettes in the United States have found little, if any, effect of such warnings. Although some have argued that this is because of the high cost of dealing with warning labels, effects are small even when individuals have read and understood the labels. [Hanson, 2003: 2014, and references] However, this could likely be because the government agents who mandate the warning labels overestimate people's demand for such warnings.

If regulators who have the power to regulate information compel private agents to be too risk averse in their communications, it is likely that the same will occur when regulators obtain the power to ban products. Even estimating the net effect of such regulation is extremely challenging. It assumes that there is a social good that can be measured by trading off lives lost with lives saved, which cannot be done given that each individual is willing to undertake different risks. [Higgs, 1994: 1-4] (Readers will note that such analyses are forthcoming in this paper. However, this is only necessary because the government has forcibly socialized this issue by automatically banning new medicines, forcing otherwise unnecessary trade-offs between different groups of patients.) Even if two patients have exactly the same, accurate understanding of the

risks and benefits of a given medicine, one may choose to take it and the other avoid it, because the latter is more averse to the risk and values the benefits less. Therefore, the costs and benefits of Health Canada's regulations do not accrue to society at large but to specific individuals. For example, patients with terminal diseases often demand new therapies faster than regulators can approve them, because the cost of therapeutic failure to those patients is very low, given their condition. [Tabarrok, 2000: 27]

The cost to the government and its agents of allowing patients to use the medicines they think they need is high, however, especially in a democracy. The majority of Canadians are not affected by the government's decision to ban any single new drug. However, they exert political pressure. Especially in a crisis, the poorly informed majority, who will not experience the consequences of their influencing the government to impose more intervention and regulation, will motivate the government to make decisions that reduce the welfare of affected patients. Furthermore, the minority who are affected negatively by a government ban are unlikely to be able to retaliate against the government's action. Health regulators have to make trade-offs between welfare of society or its individuals (which they cannot measure) and the welfare of the regulators themselves and the members of government.

### Incentives for regulators—Type-I and Type-II errors

Incentives facing the regulators who are supposed to manage pharmaceutical risk on behalf of patients lead them to impose too much safety (of one type) by denying "risky" products. [Higgs, 1994: 1–4] Unfortunately, this harms patients' welfare. To combine the language of bureaucratic incentives with that of statistics, Health Canada can make two types of mistakes. A Type-I error occurs if the regulators approve a product which later proves to have such negative consequences that it is pulled from distribution. A Type-II error occurs if the regulators deny approval for a medicine that would have had net beneficial effects to Canadians' health. These two errors both have negative consequences for patients but the consequences to the government and its agents are different. The public receives different information about the two types of wrong decisions. A Type-I error brings the wrath of the Media and a focused public upon the heads of the government. Take, for example, the following statement introducing an article on drug safety in *Business Week*: "It is almost a grim routine by now: After the Food and Drug Administration gives the go-ahead for a new drug, the product is yanked from the market when some unforeseen problem arises." [Barrett, 1998: 21] As shown below, this claim is extremely dramatic by any reasonable standard.

Type-II errors, on the other hand, both harm patients in the short run and reduce competition in a given therapeutic area in the long run by discouraging research and development in it. However, the public is unlikely to be aware of such an error. Only

companies and researchers that have been harmed by the error will concentrate on the issue. In the absence of an energetic group of advocates for affected patients, public opinion is unlikely to be inflamed, because nothing has changed from what had existed before. The loss to patients is not nearly as obvious as it is for Type-I errors. [Campbell, 2000: 314; Kazman, 1990: 40; Miller, 2000: 44; Tabarrok, 2000: 39]

Indeed, the public at large, even many physicians, are unaware of what new medicines are in the system. [Hansen, 2000: 279] (This is partially because manufacturers are not allowed to inform them.) They are even less aware of which drugs are not being invented (lost) because drug-makers respond to regulatory bias. When a drug that might have benefits is abandoned, we have only uncertainty and a lack of information. Even if a new drug reduces mortality from 30% to 20%, no one can predict who will belong to the 10%. Therefore, the earlier the government kills a promising new drug, the more difficult it is for potential beneficiaries to identify themselves and organize to resist the government's intervention. However, if an approved drug kills someone, the victim is clearly identified. [Hansen, 2000: 280]

Of any sample of large drugs on which development has begun, a number of them will have been abandoned because of ineffectiveness or harm. From those that are eventually marketed, there will come both benefit and harm. However, we do not know what benefits those that were abandoned might have provided, because their manufacturers obviously cannot communicate their benefits. [Peltzman, 1973: 1062] As one American policy analyst has said of the uphill battle to motivate the general public to resist pharmaceutical overregulation: "Those who must rely on hypothetical benefits in the debate about new drugs are at a distinct disadvantage against those who can point to real and dramatic evidence of the harm that drugs occasionally do." [Helms, 1981: xxii-xxiii]

In Canada, cabinet ministers are usually not physicians or scientists. Indeed, the last four (at least) Health Ministers: Dosanjh, Pettigrew, McLellan, and Rock, have all been lawyers. Therefore, they are highly subject to information asymmetry. The advice of civil servants within Health Canada is likely to be acceptable to the cabinet unless it carries a high cost politically. Otherwise, the governing politicians really have no need to seek out contrary information. In the United States, where the executive and legislative branches are divided, the Secretary of Health & Human Services and his senior bureaucrats are compelled to justify their actions in front of Congressional committees. Congressional agencies have conducted many studies discussing the effects of the growth of the FDA's regulatory activities. [Miller, 2000: 45-46, and sources] However, our Parliamentary system lacks this transparent struggle between political interests, so there is little counterweight to the incentives to make Type-II errors and the ministry is unlikely to act in the patients' interests.

Furthermore, some serious side effects do not become apparent until after a drug has been approved. Unfortunately, people often respond to newly discovered

information about the risks of a medicine by calling for even more testing before bans are lifted. Such calls ignore the diminishing marginal utility of testing. The most valuable information about a new medicine is that subjects did not drop dead on the first day of a clinical trial. [Higgs, 1994: 12] This first hurdle is also relatively cheap to overcome. More testing for safety and efficacy comes at increasing marginal cost for less marginally valuable information. Nor is the government capable of knowing how much information each patient wants, nor at what cost. If manufacturers were forced to do only the degree of testing that patients required, we would expect them to start selling their new medicines earlier and continue testing subsequently, in the hope of capturing patients who are more risk adverse than the initial users.

Lengthening the time new medicines are automatically banned would only reduce the timeliness of new information about their possible adverse effects. No matter how encompassing a clinical trial is, there is no way that it can determine every possible risk that patients will face once the general population starts using the drug. Testing according to government regulations is already very expensive. For a trial of 2,000 to 3,000 subjects, only adverse drug reactions (ADRs) occurring in at least one in a 1,000 cases will be considered significant. A trial would need 16,000 subjects to have an 80% chance of identifying all ADRs occurring in one in 10,000 people. [Brown et al., 2001] Once doctors are free to prescribe them, many drugs are used by millions of people. We can never be certain that we have learned every risk about a medicine, until the last person on earth has taken it.

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## Slowness does not equal safety—evidence

There is evidence, of course, that shows that prescription drugs used today continue to have some harmful effects, despite over-regulation. This is unavoidable. However, even if we accept the notion that there is some socially optimal balance of risk and return for prescription drugs (which cannot be), it is still clear that there is a net benefit in a speedier removal of the ban on new drugs. Most of this evidence comes from the United States.

### Do faster approvals mean careless examinations?

One organization that argues against the faster approval times brought about in the United States by the Prescription Drug User Fee Act (PDUFA) is the self-styled consumer advocacy group, Public Citizen/Congress Watch. According to this group, faster approvals occur because the FDA is no longer doing its job adequately and allowing unsafe drugs into the American health-care system. Public Citizen/Congress Watch reported that nine new medicines that the FDA licensed in the eight years from 1993 to 2000 had to be withdrawn. In comparison, only five had to be withdrawn in the previous eight years, before the FDA started to receive user fees to fund faster examinations of new drugs. [Public Citizen/Congress Watch, 2002] Presented this way, the higher rate of withdrawals certainly appears startling: an increase of 80%! However, a lot of the shock comes from seeing the risk reported relative to the previous period's number of withdrawals rather than as a share of the drugs approved in the period in question. Reports from non-partisan US government agencies tend to report the latter way.

The US government's auditor reported the less scandalous figures that withdrawal rates for the eight years previous to PDUFA's passing in 1992 were 3.10% compared to 3.54% for the subsequent eight years: an increase in withdrawals of less than one half of 1% of new drugs approved. Furthermore, some were removed because patients and doctors did not use them correctly rather than because they demonstrated rare side effects not discovered during trials. [US GAO, 2002: 4] Even though the increase reported was not very dramatic, the FDA found it necessary to respond to the auditor's report, pointing out that the change was not statistically significant. [US GAO, 2002: 7]

In another report by a non-partisan US government agency, the Office of the Inspector General of the Department of Health & Human Services presented similar figures. [Table 5] Importantly, this analysis also showed the withdrawal rate according to the fiscal year in which the manufacturers applied to have the ban on their new drugs lifted. This more clearly shows the effect of PDUFA than analyses based on the year of approval. Although the rate increased a little bit in the five years after PDUFA,



**Table 5: Rate of new molecular entities withdrawn from US market, by five-year period**

Period	1983–1987	1988–1992	1993–1997	1998–2002
Calendar year of approval	3.7%	2.5%	3.6%	1.7%
Fiscal year of receipt	2.7%	2.6%	3.1%	2.3%

Source: [Rehnquist 2003: 35–36](#).

it dropped again the next half decade. However, neither of these two non-partisan reports shows a statistically significant change in withdrawal rates before and after PDUFA. (Also note that both reports use periods of multiple years for analysis. Using annual periods would show zero withdrawals for several years.)

Despite the lack of evidence of increased drug withdrawals due to PDUFA, Public Citizen/Congress Watch has argued that many of the FDA’s own reviewers think that the performance requirements associated with user fees made the agency too willing to approve new drugs quickly. Two physicians associated with Public Citizen/Congress Watch surveyed the FDA’s medical officers, collecting the responses anonymously to protect the respondents. They reported that 31% (53) of the 172 medical officers responded. Of these, 19 reviewers identified a total of 27 drugs that they thought should not have been approved; 12 examiners thought that 25 drugs had been approved too fast. [\[Lurie and Wolfe, 1998\]](#) However, the number of unsatisfied medical officers responding was really quite small and the reports on withdrawals discussed above do not support the allegations.

Two subsequent reports by non-partisan government offices demonstrate more classical complaints by disgruntled examiners. The government’s auditor found that, since PDUFA, the FDA’s reviewers had increased their workload, experienced higher attrition than other government agencies, and did not undertake professional development to the degree recommended by the agency. [\[US GAO, 2002: 18–24\]](#) In another survey, to which subjects responded anonymously, some reviewers expressed concerns about the increased speed of approvals and the time-pressure since PDUFA. However, 78% were confident in the decisions that the FDA made with respect to a drug’s efficacy and 70% were confident in the FDA’s labeling decisions. Furthermore, this survey had a 47% response rate, much higher than the survey conducted by Public Citizen/Congress Watch. [\[Rehnquist, 2003: 6–17\]](#)

## Support for quicker approvals

Outside parties closer to those who are affected by the FDA’s intervention have a more favourable judgment of the FDA’s new standards but would like to see even quicker approvals. In a survey in 2002, sponsored by the Competitive Enterprise Institute, of 160 American oncologists, 48% said that the FDA had improved its approval of new

drugs and devices. Nevertheless, 61% agreed totally with the statement that the FDA was too slow to approve new drugs and devices, whereas only 37% disagreed totally. The numbers were almost exactly the same (60% versus 39%) for the statement that the FDA forced patients to go without potentially beneficial therapies. However, the oncologists thought that only 24% of the general public understood the human cost of the FDA's processes and that 70% did not understand at all. [CEI, 2002] A previous survey of 200 emergency-room physicians in the United States found similar results: 64% of those surveyed agreed totally that the FDA was too slow to approve new drugs and devices and 73% agreed that the general public did not understand the costs. [CEI, 1999]

Professors Rawson and Kaitin, as discussed above, analyzed approval times for new drugs in Canada and the United States for the 10 years, 1992 to 2001. They also examined drugs that manufacturers withdrew from the market because of safety concerns. Manufacturers withdrew 12 (11 voluntarily) of the 337 drugs that the FDA had approved in the United States. Of those 12, the slower Health Canada had approved five before the drug was pulled from the American market. Of the other seven drugs, manufacturers had applied to Health Canada for approval of five. Another drug, approved in Canada, but not in the United States, was also withdrawn from Canada. Therefore, Health Canada let one “dangerous” medicine get through while preventing five from getting through. This may lead us to believe that Health Canada is more thorough than the FDA. However, the time lag alone caused the different rate of withdrawals. All of the information that caused the withdrawals in the six Canadian instances was generated from foreign countries and Health Canada was responding to actions initially taken outside this country. [Rawson and Kaitin, 2003: 1405–06]

Furthermore, the figures reported show that 2.0% of new drugs approved in Canada are subsequently withdrawn, whereas the figure for the United States was 3.6%. This also makes it look like Canada does more thorough reviews than the United States does. However, such a conclusion confuses the average rate of withdrawals with withdrawals at the margin. Primarily because of the drug lag, Health Canada only approved 295 drugs (for which the researchers could determine the approval date). Of these, the US FDA had not approved 27, leaving 268 approved in both countries. (It is not clear whether manufacturers had applied to the FDA for approval of these drugs. The following calculation assumes that they did not.) Therefore, at the end of 2001, Canadians were waiting for 69 drugs that had already been approved by the FDA, which had approved a total of 337 drugs. Assuming that the rate of withdrawals remained the same, Health Canada “saved” Canadians from 3.6% of the 69 drugs that were “unsafe”: fractionally less than 3 drugs. On the other hand, Health Canada had deprived us of fractionally more than 66 of the drugs that were “safe”: a ratio of about 27 to one.

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## Adverse effects of approved drugs

### *Prepulsid™ (cisapride)*

Of course, we should not be fooled into thinking that drugs are “safe” just because a government regulator says so. Sometimes medicines are found to do the opposite of what is claimed. For example, in the late 1980s, physicians prescribed *encainide* and *flecainide*, which prevented premature beating of the heart (PVC: premature ventricular complex). The doctors believed that preventing PVC would prevent cardiac arrest in patients who had already had one heart attack. However, further research demonstrated that those two drugs were associated with increased cases of cardiac arrest. [Moore, 1995, cited in Tabarrok, 2000] A number of drugs have been in the news recently because of reported adverse events. Perhaps the best known in Canada is *Prepulsid™ (cisapride)*. The Canadian media reported heavily on the withdrawal of *cisapride* because of the Ontario government’s inquiry into the death of a young woman from complications associated with the drug. [Miljan, 2002]

Regrettably for those who argue the benefits of Health Canada’s slower time to approval, *cisapride* has the unfortunate distinction of being the only drug of the five withdrawn from Canada during the 10 years, 1992 through 2001, that the Canadian government approved before the United States did: August 1989 versus July 1993. Furthermore, American pharmacies stopped dispensing the drug in July 2000; whereas prescriptions were filled in Canada until August. [Rawson and Kaitin, 2003: 1406] The FDA banned *cisapride* after linking its use with irregular heartbeats in 340 people, of whom 80 died. [Henderson, 2002: 189] However, Health Canada had reported adverse reactions in the *Canadian Adverse Drug Reaction Newsletter* as early as July 1996 and the manufacturer claims to have first sent advisory letters to Canadian physicians and pharmacists in 1995. [Arnott, 2001; CMAJ, 2001] [2]

However, even the banning of a drug after previously unknown hazards have become apparent is fraught with risk. Lost in the outcry by the Media was the information that *cisapride* also benefited many patients. Although *cisapride* was associated with 44 reported cardiac arrhythmias here, Canadians had filled 7.7 million prescriptions. [CMAJ, 2001 and references] By the time it was taken off the market in Canada, physicians were writing one million prescriptions annually. [Miljan, 2002] The warning letters had not dissuaded physicians from prescribing it because the risk of death was small. One expects that physicians would have informed their patients of the small but catastrophic risks of this drug before prescribing it, as is their professional responsibility. Unfortunately, its removal caused other patients, for whom *cisapride* was very beneficial, to suffer. The press reported the story of one patient in the United States who could no longer digest without pain. The FDA now allows such patients to continue to use *cisapride* but only under certain criteria and while

enrolled in special studies. [Henderson, 2002: 189] This case is a sterling example of the bias that prefers Type-II to Type-I errors in the regulatory state.

#### **Lotronex™ (alosetron HCL)**

Another drug that drew the attention of the Media was Lotronex™ (*alosetron HCL*), used for irritable bowel syndrome. In the United States, the manufacturer took Lotronex™ off the market on November 28, 2000, at the FDA's urging. About 300,000 patients were taking the drug and the FDA responded to reports of 70 cases of severe constipation or ischemic colitis (lack of blood flow to the colon), because of which five deaths occurred. Several thousand patients contacted the FDA and manufacturer after the withdrawal, demanding it back, and furious at Public Citizen/Congress Watch for advocating its withdrawal. [Grady, 2001] Fortunately for them, it has since come back on the market.

#### **Halcion™ (triazolam)**

Governments have often acted to remove drugs from the market upon learning of catastrophic adverse events associated with their use, even if the absolute risk is small. One controversial psychiatric drug is Halcion™ (*triazolam*), one of a class of drugs known as benzodiazepines, which were heavily used in psychiatric treatment during the 1970s. Starting in 1979, doctors in Holland and the United Kingdom reported adverse psychiatric events for patients on the drug. However, even though the relative risk of adverse events was quite high, the absolute risk appears a lot less startling. In the United Kingdom in 1986, 2.5 adverse psychiatric reactions per million prescriptions were reported by the Committee on Safety of Medicines, compared to between zero and 1.9 for patients taking other benzodiazepines [Abraham, 2002b: 1677], a relative difference of about one third but an absolute difference of between 0.6 and 2.5 percentage points.

#### **Vioxx® (rofecoxib)**

A more recent example is Vioxx® (*rofecoxib*), which was approved in the United States and Canada in 1999 and soon became a sales blockbuster. Vioxx® was used for arthritis and had the reported advantage of reducing the risk of gastrointestinal (GI) complications among those who suffered stomach ulcers and related problems when using Non-steroidal anti-inflammatory drugs (NSAIDs). However, subsequent research demonstrated that Vioxx® increased the risk of cardiovascular problems such as heart attack and stroke. Because of these risks, Merck withdrew Vioxx® on September 30, 2004, causing its stock price to decline by about a third. Soon after, Pfizer made public information suggesting similar issues for its competing drug, Celebrex® (*celecoxib*) but Pfizer has chosen to not withdraw its product from the market. [Pfizer, 2004a, b]

Merck took its action as a result of the APPROVe trial, a study of Vioxx<sup>®</sup> on subjects with colon polyps. In this trial of 2,600 subjects (who were screened not to have cardiovascular disease), 3.5% of the Vioxx<sup>®</sup> subjects had a heart attack or stroke versus just 1.9% of those on placebo. [Topol, 2004] APPROVe's negative results appeared 18 months after the trial began. [Merck, 2004a: 4] The outcomes caused the company to cancel the trial and two others, as well as to withdraw Vioxx<sup>®</sup>.

Merck consistently claims that it has disclosed its research results in a timely manner. The firm claims that results of research prior to the APPROVe results in September showed no difference in confirmed cardiovascular event rates between Vioxx<sup>®</sup> and placebo or NSAIDs other than *naproxen*. [Gilmartin, 2004a, b] On the other hand, some in the medical community claim that other studies demonstrated these risks adequately enough years before and that the drug should have been withdrawn much earlier. [Topol, 2004]

In March 2000, data from the VIGOR trial, which compared Vioxx<sup>®</sup> to *naproxen* on patients with rheumatoid arthritis, showed increased cardiovascular events for subjects on Vioxx<sup>™</sup>. However, Merck was not sure whether naproxen had a beneficial effect (like aspirin) or Vioxx<sup>™</sup> a detrimental one. Two previous trials of Vioxx<sup>™</sup> versus a placebo on Alzheimer's patients showed no difference in cardiovascular events. Nevertheless, this resulted in the company changing its prescribing information to show the potential risk of heart attack and stroke. [Gilmartin, 2004b]

After the withdrawal, *The Lancet* published a so-called meta-analysis reviewing 18 randomized controlled trials and 11 observational studies that examined Vioxx<sup>®</sup>. In total, there were 21,432 patients, who suffered 64 heart attacks. Of these, 52 took place in subjects using Vioxx<sup>®</sup> and 12 in the control groups. In a smaller set of studies in the analysis (number of subjects unreported), the groups using Vioxx<sup>®</sup> suffered 25 strokes and the control groups, 19 strokes. Similarly, a sub-set of nine studies reporting death from cardiovascular events showed 18 deaths in Vioxx<sup>®</sup> groups and 13 in control. In 17 studies that reported overall "serious cardiovascular events," 85 such events occurred in the Vioxx<sup>®</sup> groups and 38 in control groups. The authors argue (with the benefit of 20/20 hindsight) that the meta-analysis contradicts Merck's claim that adverse events only arise after 18 months. [Jüni et al., 2004: 2025] They also argue that the subjects in the studies that they analyzed were less prone to heart attacks and stroke than patients in ordinary clinical practice, because of the way the trials were designed. [Jüni et al., 2004: 2027]

This is not a debate that this paper will attempt to resolve, nor is the author qualified to do so. However, it does show the benefits of continuing to do research after a drug is on the market and of having a vigorous professional debate about it rather than banning it outright. In fact, knowledge about the negative effect of Vioxx<sup>™</sup> is only the result of very long-term research: Vioxx<sup>®</sup> and aspirin are the only two NSAIDs with significant, long-term, public data about their safety. [Gilmartin, 2004b]

### *The benefits of Vioxx®*

Let us accept that there is an increase in the risk of a heart attack or stroke from using Vioxx™. This does not automatically mean that the government should ban it. An estimated 15,000 Americans die each year from gastrointestinal complications associated with the use NSAIDs. [Gilmartin, 2004b] Many of those patients might willingly choose the increased cardiovascular risk of Vioxx®, given its other benefits.

The original published study, VIGOR, reported that Vioxx® reduced the risk of a gastrointestinal event by one half: from 4.5 to 2.1 per 100 patient years. On the other hand, the control group (taking *naproxen*) suffered significantly fewer heart attacks than the Vioxx® group: 0.1% versus 0.4%. In other words, the relative risk ratio for improving gastrointestinal outcomes was 0.5, whereas for heart attack was 0.2. [Bombardier et al., 2000] It is far from obvious that a well-informed patient, at low risk for a heart attack or stroke but high risk of GI complications from other NSAIDs, would not choose Vioxx®. Furthermore, Vioxx® was being studied for other uses when Merck withdrew it. Indeed, it was withdrawn as a result of a study on its effect on colon polyps. Now that it is withdrawn, and all trials stopped, many potential benefits will be lost. Merck's CEO stated that the firm considered keeping Vioxx® on the market, with a new label, but, since the alternatives on the market gave satisfactory choice to patients, decided to pull the drug. [Gilmartin, 2004b] One cannot help but think that, if Vioxx® was still available, many more patients would benefit from it than suffer.

## Improving information about drugs

These examples are not to make a layman's argument that health professionals and patients should ignore the serious risks associated, albeit infrequently, with these and other medicines but to point out that the evidence and quality of information about a drug can be improved without the government's banning its use. Recently, Dr. Lance De Foa, a Canadian GP, reacted critically to Health Canada's decision to take steps to eliminate medicines with the ingredient *phenylpropanolamine* (on the grounds of increased risk of hemorrhagic stroke). Dr. De Foa noted that millions of patients have used medicines containing *phenylpropanolamine* without incident and that the US FDA has reported only 60 cases of hemorrhagic stroke since 1969. [De Foa, 2002] Again, we see the overly cautious avoidance of Type-I errors in favour of Type-II errors that are likely to be more harmful overall because of foregone benefits that patients would enjoy if they were able to use the banned medicines.

Of course, even medicines that do not make the headlines offer the risk of adverse events. In an article suggesting that the FDA's faster approval times potentially increased the supply of risky medicines, Lasser *et al.* [2002] found that of 548 new chemical entities approved by FDA from 1975 to 1999, 10.2% subsequently received

“black box” warnings (that is, warnings that are printed so boldly on the label that they are impossible to ignore) or were withdrawn. Only 16 (2.9%) were withdrawn. However, the flipside of this is that 90% did not receive such warnings and 97% were not withdrawn!

A previous analysis, by the US government auditor, reported results that appear even more cautionary. It found that, of 198 drugs approved by the FDA between 1976 and 1985, 102 (52%) had serious risks (including side effects that could lead to hospitalization, severe or permanent disability, or death) that were determined after the FDA had approved them. These led to changes in labeling that limited the appropriate populations or added warnings or precautions. [US GAO, 1990] However, all but six were still on the market as of September, 1989 because, as the report noted, “the number of serious postapproval risks is small when compared to the number of adverse reactions that had been identified at the time of approval.” [US GAO, 1990: 3] Nonetheless, while recognizing the risks of misprescribing and adverse events, the US Department of Health & Human Services was horrified by the report, fearing that it would alarm patients and cause them to avoid valuable medicines. [US GAO, 1990: 26–27, 119–23]

Furthermore, we do not really know how many adverse drug reactions (ADRs) are occurring today. In a paper published in 2001, Dr. William Kelly reviewed MEDLINE (an index of published medical literature) and found 20 studies plus one meta-analysis that reported adverse drug reactions. Perhaps unsurprisingly, given the difficulty of gathering data on ambulatory patients, 14 of the studies were conducted on patients in hospital. The articles reviewed found a range of prevalence of fatal adverse drug events from zero to 2.3%. Dr Kelly concluded that there is no good estimate of the systemic number of fatal adverse events in the United States. [Kelly 2001]

### **Information about ADRs in Canada**

The lack of information on ADRs is also of concern to the Canadian medical community. On May 1, 2001, inspired partially by the history of *cisapride*, the *Canadian Medical Association Journal* (CMAJ) announced that it would publish warnings from the FDA as well as Health Canada because Health Canada lagged the American agency in disseminating reported ADRs. [CMAJ, 2001] The CMAJ also called for tighter regulation of the information leaflets that patients receive with their prescriptions.

Currently, physicians in Canada report ADRs voluntarily; therefore, it is unlikely that there are satisfactory incentives for optimal communication of ADRs. Information about ADRs has a significant external benefit to those other than the patient who suffers an ADR and the doctor who observes it. The purpose of this paper is not to discuss how to structure such incentives but to argue against the Canadian government's automatic banning of new medicines. Therefore, it suffices to say that the current regulatory intervention diverts resources away from improving the incentives for optimal reporting of ADRs in favour of requirements that have negative marginal returns to

Canadians' health, namely, the onerous burden of having the automatic ban on using a new drug lifted. In order to improve the reporting of ADRs, Health Canada is developing the Canadian Medication Incident Prevention Reporting System in conjunction with the Canadian Institute for Health Information and the Institute for Safe Medication Practices Canada. [Health Canada, 2003; 2004; O'Reilly, 2004] However, of the \$31 million allocated to improve Health Canada's regulatory processes for 2003/2004, only \$2.5 million went to marketed health products, that is, post-market surveillance of medicines used in the community. [Lexchin, 2004]

### ***Errors in prescribing medicines***

The negative effects of prescription drugs are not due only to the therapeutic molecules within them but sometimes also to mistakes made by health professionals or patients. According to David U, President and CEO of the Institute for Safe Medication Practices Canada, medication errors cause 700 deaths annually in this country. [O'Reilly, 2004]

Nevertheless, we also know that many physicians and patients are content to use prescription drugs for purposes other than those authorized by government agencies such as Health Canada. Once the government lifts its ban on a new drug, physicians often prescribe it for conditions other than those approved by the government, which is perfectly legal. This "off-label prescribing" is very common in the United States, where most pediatric patients and many AIDS and cancer patients receive prescriptions for drugs that the FDA has not approved for their conditions. [Tabarrok, 2000: 26, and references] There is no reason to expect Canadian physicians to behave differently. MEDLINE, the index of medical literature mentioned above, has a drug database on the Internet that lists off-label uses for prescription medicines. Through off-label prescribing, physicians and patients inform us that they consider themselves capable of judging when to use a given medicine, whether or not the government has approved it.

Patients also react quickly to privately generated information in the absence of the government banning a therapy. By January 2003, within six months of the release of a study that demonstrated that hormone replacement therapy (HRT) appeared to do more harm than good for most women (by increasing the risks of breast cancer, stroke, and other ailments), 44% of Canadian women who had been taking HRT had stopped and another 32% said that they were planning to do so, according to a poll of 500 Canadian women over the age of 50 years. [Picard, 2003]



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## Losing the benefits of new medicines

So far, we have looked at the negative health effects of prescription drugs and found them to be less harmful than supposed when reviewed uncritically. Furthermore, we have seen that the government is likely to ban medicines to such a degree that the harm avoided by the ban is far less than the benefits that patients would enjoy if they were able to use the banned medicines. Fortunately, there is a body of research on the health benefits of prescription drugs (at least, those that the government does permit) that allows us to estimate the net harm to patients of the current policy.

Not all of our increased life expectancy in recent years is due to prescription drugs, but much of it is. For example, a number of innovations in treatment have contributed to superior outcomes after heart attacks in the United States. From 1984 to 1998, the life expectancy for elderly heart-attack patients increased by one year, even though the frequency of heart attacks stayed about the same. Between 1975 and 1995, about one third of the increase in life expectancy for heart-attack victims was due to increased use of aspirin, a drug invented and marketed in the nineteenth century. Surgical procedures (such as angioplasty) reduced the likelihood of death within two years by about a quarter. However, about 17% of the improvement was due to “clot-busting” drugs introduced during and since the 1970s. [Gowrisankaran, 2002, and references] Therefore, because of Canada lags the United States by a number of months in approving new drugs, we can conclude that Canada’s banning new medicines did not just inconvenience patients; it unnecessarily shortened their lives.

### Research showing the harm of automatic bans on new medicines

In an extremely thorough analysis of international data on health spending, Professors H.E. Frech and Richard D. Miller examined the effect on life expectancy of increased spending on different health services in 1985 for a number of different countries. Table 6 shows data for Canada, the United States, and the United Kingdom. For a 60-year-old Canadian woman one extra dollar (US) of spending on pharmaceutical use explained an increase in life expectancy of 2.27 days. For a Canadian man of the same age, the increase was 1.8 days. As discussed above, around this period, Canada took about two years to approve new medicines for distribution, while the United Kingdom took about half a year, and the United States either about a year (for major advances) or a year and a half (for minor advances). [Goyer, 1986: 37] Note that Frech and Miller did not specifically demonstrate the superiority of new drugs over older ones (because they did not use any explanatory variables for the vintages of drugs

**Table 6: Days of life added per US dollar spent on pharmaceutical consumption in three countries at three ages, 1985**

	Female			Male		
	Birth	40 years	60 years	Birth	40 Years	60 Years
Canada	0.946	1.704	2.272	0.873	1.488	1.832
United States	0.784	1.390	1.820	0.719	1.212	1.501
United Kingdom	0.935	1.643	2.081	0.872	1.443	1.691

Source: [Frech and Miller 1999: 48](#).

used) but rather the value of spending on drugs in general. Therefore, there is no apparent connection between drug lag and the variation in relative benefits of medicines across the three countries.

In a similar effort, a team from a private research group, led by Dr. Pierre-Yves Crémieux and Professor Pierre Ouellette of the Université du Québec à Montréal, conducted an examination, funded and published by the Canadian trade association for brand-name pharmaceutical manufacturers, of the value of pharmaceuticals in Canada. [[Analysis Group/Economics, 2002](#)] Examining the effects of changes in spending on health services in Canada from 1981 to 1998, these researchers determined that increased spending on drugs explained significant increases in three health outcomes: reduced infant mortality, life expectancy at birth, and life expectancy at age 65. [Table 7](#) summarizes the results. For example, a 1% increase in government pharmaceutical spending on newborns decreases infant mortality for girls by 0.14% whereas an increase in private spending explained a decrease in male infant mortality of 0.17%. Similarly, increased pharmaceutical spending explained increases in life expectancy, both for newborns and seniors. [[3](#)] As with Frech and Miller's international research, this analysis includes both the effects of more spending on drugs of all vintages, not just on new drugs, so it cannot help us understand the effect of Canada's drug lag on its own.

**Table 7: Percentage increase in health outcomes per percentage increase in drug spending in Canada, 1981–1998**

	Female			Male		
	Infant mortality	Life expectancy at birth	Life expectancy at 65 years	Infant mortality	Life expectancy at birth	Life expectancy at 65 years
Government spending	-0.143	0.009	0.012	-0.108	0.011	0.029
Private spending	-0.161	0.006	0.018	-0.169	0.015	0.054

Source: [Analysis Group/Economics 2002: B-17](#).

Note: All co-efficients significant at  $p < 0.05$

Peltzman, discussed above, estimated that the costs of government-imposed delays preventing patients from using new drugs in the United States were far greater than the benefits derived from avoiding side effects of those drugs. Having calculated the drug lag, using econometric tools, he estimated that the delay cost patients \$350 million to \$450 million (US) in lost benefits, in exchange for about \$100 million worth of adverse events avoided: a net loss of about four to one, from 1963 through 1970. [Peltzman, 1974] A decade later, when the drug lag in the United States was at its longest, Dale Gieringer of Stanford University examined the consequences on mortality of the FDA's lengthy drug-approval times. [Gieringer, 1985] This approach has the benefit of not requiring an estimation of how much other people value their health but simply works with the reasonable assumption that people would prefer to be alive rather than dead. By looking at the difference between casualties from prescription medicines in the United States and those in less regulated countries, and comparing that to reductions in mortality for diseases where drugs are known to play a major role in improving outcomes, he concluded that the costs of delayed drug approval in the United States far outweighed the benefits.

Examining new drugs introduced in the United States between 1950 and 1977, Gieringer concluded that the new medicines had the gross effect of reducing mortality by somewhere between 50 to 102 lives per 100,000 (or a range of 43 to 88 lives per 100,000 if tuberculosis is excluded). Therefore, delaying these drugs by just one year cost 37,000 to 76,000 lives per decade in the US population (or 32,000 to 65,000 excluding tuberculosis). The actual drug lag of between eight and 19 months led to the conclusion that the ban cost between 21,000 and 210,000 American lives per decade. However, Gieringer recognized that the FDA's ban was not the sole cause of this loss of life because other factors affected the uptake of new drugs by patients. For example, hypertensive patients in the United States were unlikely to learn of the benefits of drugs for their condition during the period, because the US government generally prevented drug makers from communicating this valuable information to them. [Gieringer, 1985: 188–89] On the other hand, because the analysis only addressed drugs that manufacturers actually launched during the period, it could not estimate the benefits that patients did not enjoy because of the drug loss due to the 1962 amendments.

Gieringer did not ignore the fatal effects of the few drugs that the FDA did allow on to the market in the United States that had unexpectedly tragic consequences. From 1950 to 1980, 11 drugs were introduced that were to be implicated in over 100 deaths or serious adverse events worldwide. The biggest killer of these was *isoproterenol*, which was associated with 3,500 asthma deaths in children, while *thalidomide* was related to over 10,000 birth defects. [Gieringer, 1985: 192] However, these tragic outcomes were over-balanced by the benefits of other medicines approved during the period. Because the FDA took longer to approve new medicines than other countries did, it saved an estimated 5,000 to 10,000 lives per decade during the period by preventing Americans

from using a handful of medicines. [Gieringer, 1985: 196] Although the wide ranges of lives both lost and gained prevent us from calculating a meaningful ratio, Gieringer's analysis informs us that the drug lag cost many thousands more American lives than it saved, a conclusion similar to that expressed by Peltzman in dollars.

Recall that the Canadian drug lag compared to that of the United States in the early 1980s was between 5.1 months and 12.3 months, depending on the effectiveness of the drug. [Goyer, 1986: 37] Assuming a Canadian population  $\frac{1}{10}$  that of the United States, we can roughly estimate that regulatory policy here cost between about 1,500 and 7,800 lost lives per decade during the period. Furthermore, between about 3,600 and 19,800 lives would not have been lost had there been no automatic ban imposed by the government.

More recently, Professor Lichtenberg of Columbia University examined US data from 1960 to 1997, and estimated a health-production function with a number of inputs. As a proxy for medical innovation, he used the number of approvals of new drugs by the FDA. The results showed that an increase in the approval rate of one drug per year explains an increase in life expectancy at birth of 0.093 years (40 days). [Lichtenberg, 2002a: 15] If this holds true for Canada, which had 331,522 births last year (according to CANSIM II), an increase in approvals by one drug per year would increase our country's life-expectancy by about 30,832 life-years each year. Canada's actual average number of drugs approved during the 10 years from 1992 through 2001, was 30 new drugs per year, that is, four less than the United States. [Rawson and Kaitin, 2003: 1404] We can very roughly estimate that, had Canada approved the same number of drugs annually as the United States did, the higher number of approvals would have increased our country's life-expectancy by about 130,000 life-years annually.

Looking at US data for three years from 1996 to 1998, Lichtenberg also determined the effect that spending on newer drugs had on other health spending. He found that a reduction in the vintage of a drug reduced non-drug medical expenditure by 7.2 times as much. [Lichtenberg, 2002b] For example, reducing the mean age of drugs used to treat a condition from 15 years old to 5.5 years old, decreased non-drug health spending by US\$129, even though it increased prescription spending by \$18 per patient (because new drugs typically are higher priced than old ones). Most of the savings were due to reduced spending on hospitals (\$80) and visits to physicians' offices (\$24). Recall that the Canadian drug lag compared to that of the United States for these three years was about 4.1 months. If the FDA had slowed down its approval times to match the Canadian drug lag, the United States would have spent about twice as much on non-drug costs as it saved by using lower-priced drugs that had been approved according to the Canadian time-frame, all other things being equal. [4] (In this case, it would not be appropriate to use Lichtenberg's estimates to determine the effect on Canadian health spending of faster Health Canada drug approvals, because the two countries conduct health spending very differently.)

Finally, Lichtenberg and Suchin Virabhak, examining US data from 1997, estimated a number of effects of using new drugs on various indicators of quality of life. Generally (but not universally), these models found that using newer drugs increased patients' health status while reducing limitations on social and other activities as well as physical limitations. Most of the models also determined that using new drugs increased the likelihood of patients living another year. [Lichtenberg and Virabhak, 2002]

## Advocates of speedier approval

Nor are these academic papers the only source of information about the harm done by governments' automatically banning new medicines. In Canada, a number of patients and groups that advocate for them are resisting the government's interference in their health care. Groups such as the Cancer Advocacy Coalition and the Best Medicines Coalition continuously agitate for speedier approval of new drugs by Health Canada. [Kondro, 2002] The Best Medicines Coalition has also bought advertisements in national Media drawing attention to patients' plight at the hands of Health Canada.

The Media periodically find an interest in reporting the consequences of the government's Type-2 errors in banning new drugs that patients value. In November 2002, a national Canadian newspaper wrote about a woman suffering from rheumatoid arthritis who had lost the ability to walk. She and her doctor agreed that she should take Enbrel™ (*etanercept*), a drug allowed in the United States since November 1998. However, the Canadian government forbade her to use it and she found that politicians had little understanding of her plight. After a year of lobbying by her and her doctor, the Canadian government allowed her a six-week supply at the end of 1999. Reportedly, she was able to walk again after three injections over a period of 10 days. However, the government did not lift its ban on the drug until December 2000. [Adams, 2002] The Media also paid some attention to patients who suffered from the government's delay in lifting its ban on Remicade™ (*infliximab*), a competing medicine for rheumatoid arthritis. According to the President of the Canadian Arthritis Society, appropriate use of this drug could get patients out of wheelchairs and moving on their own again. [Sokoloff, 2001] [5]

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## Conclusions

The Canadian government takes a longer time than governments of comparable countries to lift its automatic ban on new medicines. Evidence shows that the policy of automatically banning new medicines harms Canadians far more than it helps them. The net cost of this policy is that hundreds of Canadians likely die every year while more continue to suffer needlessly because the government prevents them from taking the medicines they need.

Despite a decade of user fees, paid by drug makers to increase the budget available to Health Canada, the department has not improved its performance in comparison with comparable countries that similarly have user fees; and its recent performance has even deteriorated against what it was achieving in the late 1990s. A recent law passed to address this failure, the User Fees Act, is not likely to improve the situation because it does not increase Canadians' freedom to choose medicines that the government does not permit.

Health Canada is unlikely to be able to increase its budget to levels comparable to that of the US FDA because Canada is a much smaller country. Therefore, it is unlikely that increased domestic user fees or taxes will free Canadians from their government's dangerous delays in approving new medicines. In comparison to other countries' regulators, who also have many fewer resources for pharmaceutical regulation than does the United States, Health Canada is extremely unproductive. Its pharmaceutical regulatory output is 38% that of Sweden and about half that of the United Kingdom and Australia. Because Health Canada does not face competition in earning user fees for certifying the safety and effectiveness of drugs used by Canadians, as regulators in the European Union do, it faces little incentive to improve its own performance without external pressure.

In the absence of a change in the climate of public opinion, the Canadian government is unlikely to improve the current policy, because the harmful errors made by Health Canada are unlikely to reach a broad audience and have little political cost.

Theory and anecdotal evidence, as brought forward by representatives of the Canadian medical profession, suggest that the incentives for optimal communication of harmful side effects (ADRs) of drugs that are already being used in Canada are not adequate. Valuable resources are wasted overcoming the automatic ban on new drugs, some of which might be better directed to improving the quality of information about the risks and benefits of drugs once they are in use.

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## Options for Reform

### Replace the government's regulators with private certification

One option for reform, and the one that most increases Canadians' freedom to choose their medicines, is simply to get rid of the whole regulatory enterprise. In this case, manufacturers would have the sole responsibility of convincing physicians and patients that they should use any new drug. Those physicians and patients would likely demand that manufacturers submit their new drugs to private bodies, likely non-profit, to certify their risks and benefits. As suggested by the greater relative productivity of the British and Swedish pharmaceutical regulators, who operate in a quasi-competitive environment, this would also increase the productivity of those certifying the results of the testing.

This option derives from actual practice in other areas of risky human endeavour. One example is Underwriters' Laboratories (UL), which has certified products for much longer than Health Canada: it was founded in 1894 as an independent, non-profit organization. Underwriters' Laboratories receives no tax-revenue and yet certifies tens of thousands of different products in areas such as electrical safety, fire suppression, and liquid gas. Indeed, its many thousands of clients include government agencies. No law requires certification by Underwriters' Laboratories but governments accept UL certification for many areas in which they regulate standards. [Campbell, 2000: 337-40]

Another example is the Snell Memorial Foundation (SMF), founded in 1957 by friends of William "Pete" Snell, a race-car driver who died of head injuries sustained when his helmet failed to protect him. SMF was motivated by the goal of improving the effectiveness of helmets and now sets standards for all types of helmets. Many people engaged in activities such as mountain biking, for which helmets are an important safety feature, value the SMF certification and this motivates manufacturers to submit their helmets for testing at their own cost, although there is no legal requirement to do so. SMF limits itself to the business of researching and testing the effectiveness of helmets. It does not advocate mandatory helmet laws and has never lobbied on any pertinent legislation. According to the SMF, its standards surpass those of the US Department of Transportation and US Consumer Products Safety Commission. [Snell Memorial Foundation, 2004]

This method of certification has two advantages. First, because private certifiers operate in a competitive environment, they would be more productive than the status quo, where Health Canada enjoys a government monopoly. Second, private certifiers would likely recognize a range of standards for safety rather than the current "one size fits all." [Campbell, 2000: 333] This means that Canadians who prefer to accept more

risk with their medicines would be able to act on earlier, less complete, information about the effects of a new medicine. On the other hand, Canadians who are more risk averse could wait for a higher standard of certification that would result from more expensive and thorough testing. The Canadian government would not compel any patient to accept another's standard of safety.

## Reciprocity with regulators in other countries

If the use of private certifiers were adopted, Health Canada would evolve from a certifier of products to a certifier of certifiers. In this respect, it would largely return to its earlier role: ensuring that products are not misbranded or adulterated. [Miller, 2000: 71–73, 90–101] However, given that every comparable country has a national pharmaceutical regulator with some degree of monopoly power (although the EU has some intra-EU competition), it would be too much to expect Canada to set the pace in moving to private certification. Therefore, a middle ground would allow Canadians to use a new drug as soon as a regulator in a comparable country lifts its ban on it. The United States, Australia, or members of the European Union are obvious candidates for such reciprocity. In this case, Health Canada would become more productive because it would compete for user fees with similar regulators in other countries. As soon as a regulator in a comparable jurisdiction lifted its ban on a medicine, Canadian patients would have the right to use it.

However, Health Canada would retain the right to compel manufacturers to label their medicines with the warning that Health Canada had not approved the safety or efficacy of the medicine. If Health Canada chose to, it could then approve the medicine according to its own time-frame, but funded only by taxes without additional user fees. If the manufacturer thought it valuable to have Health Canada remove its warning label, it could pay a user fee to have the department review and certify a drug, as currently takes place. Health Canada could also distribute its warnings that it had not approved a drug to professional publications such as the *Canadian Medical Association Journal* and through other means of communication to health professionals, such as “Dear Health Professional” letters (which are currently used to advise of ADRs that arise after a drug is distributed in Canada). Health Canada could also communicate its warnings to the general public via its website, publications, or advertisements (a right currently denied to drug-makers).

Furthermore, each physician could choose whether to prescribe drugs not actively approved by Health Canada. Provincial health ministries, Colleges of Physicians & Surgeons, or medical associations could even produce lists of doctors that did or did not prescribe medicines certified by Health Canada, so patients could inform themselves about the risks of the drugs available to them through different practitioners. After



a few years, information about the number of prescriptions written that is captured by groups such as the non-profit Canadian Institute for Health Information or the for-profit IMS Health Inc. would inform Parliament and the people how much Canadian patients valued Health Canada's input into their decisions about the medicines they use compared to input from other national regulators such as the US FDA. If Canadian patients really think that it is important for our government to stop us from using new medicines, few will ignore "would have banned" labels and we will be more confident that Health Canada provides a valuable function. If many Canadians use medicines approved by a foreign regulator, then we can move to even less regulation. Ultimately, this would include eliminating Health Canada's budget for approving new medicines.

There are a couple of caveats to this deregulation. First, patents are intellectual property rights created by national governments. There are medicines that are protected by patent in Canada that are not patented in other countries. Therefore, the Canadian government must not allow patients to steal the intellectual property of drug-makers whose medicines are still patented in Canada by approving of the use of generic medicines certified by regulators in countries where the drug is not patented.

Second, the government, as part of its role in policing misbranded or adulterated medicines, would still need to keep a watch on the border, to ensure that counterfeit drugs, or those that have been illegally misappropriated from manufacturers' distribution systems, are not allowed to enter the country. (This "parallel trade" is the subject of [Graham, 2003](#).)

Limited by the two caveats above, Canadians' health and welfare will increase if Parliament amends the Food and Drug Act to require the Minister of Health to issue a reciprocal NOC when a drug-maker informs Health Canada that comparable foreign jurisdiction, such as the United States, the European Union, or Australia, has lifted its ban on a new drug. The amendment would allow Health Canada to compel the drug-maker to put a warning label on the drug, and communicate with others that it did not actively approve the drug, as described above. If a manufacturer chooses to, it can pay a user fee to have Health Canada conduct its own certification and remove the warning label.

Furthermore, the amended Act would require the Minister of Health to make an annual report to Parliament containing information about the reciprocal NOCs issued by Health Canada under the amendments, as well as the application and removal of warning labels by Health Canada, the number of prescriptions written as a result of these actions, and reported ADRs associated with the new drugs.

After a period of five years, Parliament would review how Canadians responded to the amendments, and introduce further regulatory reform based on that information. This may include eliminating Health Canada's budget for reviewing new drugs itself and adding private certifying bodies to the list of those whose approval is acceptable in Canada.

## Notes

- 1 I and others have estimated the probable future drug loss that will follow proposed policies currently discussed in the United States to reduce drug-makers' profits artificially by "re-importing" cheaper medicines from Canada and other countries, or by imposing price controls. [Graham, 2003, and references]
- 2 The withdrawal dates refer to the dates when pharmacies stopped distributing the drug. According to Janssen-Ortho Inc., the Canadian subsidiary of the manufacturer of Prepulsid™ (*cisapride*), the company's last sale in Canada occurred on May 29, 2000. In the United States, the company's sales stopped on July 14. [Arnott, 2001]
- 3 It appears that this measures the effect of prescription and over-the-counter spending as well as spending on personal-care products. [See Analysis Group/Economics, 2002: A-13, B-8.]
- 4 Lichtenberg uses the natural logarithm of the vintage of the drug in years as an explanatory variable for different functions, with the dependent variables being spending on different health services (e.g. hospitals, drugs, etc.). A unit decrease in this variable (log of the age of the drug) explains 7.2 more times reduction in other health spending as the increase in pharmaceutical spending. The US drug lag over the period was 1.09 years and Canada's, 1.43 years. Their logs are 0.09 and 0.36, respectively, with a difference in logs of 0.27; and 7.2 times 0.27 is approximately equal to 2.
- 5 Of course, even these drugs are not free of risk. According to the manufacturer, trials with Remicade™ have observed more deaths from heart failure in some patients with congestive heart disease than those on placebo. [Larose, 2001] Enbrel™ has been associated with serious side effects, including death, from sepsis. [Immunex Corporation, 1999]

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## Glossary

<b>ADR</b>	Adverse Drug Reaction (negative side effect)
<b>DIN</b>	Drug Identification Number (assigned by Health Canada to every drug)
<b>EMEA</b>	European Agency for the Evaluation of Medicinal Products
<b>EU</b>	European Union
<b>FDA</b>	Food and Drug Administration (United States Department of Health & Human Services)
<b>GMP</b>	Good Manufacturing Practices
<b>HRT</b>	Hormone Replacement Therapy
<b>INDS</b>	Investigational New Drug Submission (similar to NDS but submitted before clinical trials)
<b>NCE</b>	New Chemical Entity
<b>NDA</b>	New Drug Application (from manufacturer to FDA, similar to NDS)
<b>NDS</b>	New Drug Submission (from manufacturer to Health Canada, similar to NDA)
<b>NOC</b>	Notice of Compliance (Health Canada's decision to lift the ban on a new drug)
<b>PDUFA</b>	Prescription Drug User Fee Act (United States law passed in 1992 and renewed every five years)
<b>PVC</b>	Premature Ventricular Complex
<b>SMF</b>	Snell Memorial Foundation
<b>UL</b>	Underwriters' Laboratories

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