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Risk, "Progressive Licensing" and the Health Benefits Lost by Over-Regulating New Drugs

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Executive summary

Health Canada recently posted on its website *The Progressive Licensing Framework: Concept Paper for Discussion* [Health Canada, 2007]. This paper proposed a new system of progressive drug licensing that would potentially fast-track pre-marketing approval of new medicines in exchange for greater post-marketing surveillance of drug safety. This proposal has the potential to speed up access to new medicines without sacrificing patient safety if it is built upon sound principles of risk assessment. But the proposal will further reduce access to new medicines if it is pursued without an understanding for the broader context of risk or without an appreciation of the trade off between costs and benefits linked to excessive regulation of drug safety.

Part of the rationale used to justify pre-market regulation of drug safety is that the market is not as effective as government regulators at reducing the harm that might be caused by unsafe drug products due to imperfect and asymmetric (or unequal) information between sellers (medicine producers) and buyers (patients). Specifically, consumers face an information deficit about the qualities of new drugs that leaves them exposed to potential harm. At the same time, it is alleged that drug companies might have a profit incentive to carry out insufficient clinical testing or overemphasize their product's benefits while downplaying its adverse effects. An additional assumption is that the information asymmetry facing consumers is not adequately mitigated by the presence of a physician acting as an expert agent. There is also an assumed absence of other market mechanisms—like non-governmental organizations that promote consumer product safety or publish various consumer reports—that could resolve this issue in the absence of government intervention. Therefore, it is reasoned, individuals cannot be left to use their own judgement when obtaining new medicines and a centralized government regulator should limit individual choice about the use of drugs to protect the public health. The potential harm that can be caused by an unsafe drug rises to a level of seriousness that demands pre-emptive risk reduction strategies.

However, this criticism of the market is too extreme. Approving a new drug requires regulators to make decisions with imperfect knowledge. There are significant limitations to the information that can be generated by pre-market clinical trials as well as post-market drug surveillance. Imperfect information leaves regulators in a position of uncertainty, yet there are diminishing returns from increased drug testing designed to further reduce uncertainty. To make matters worse, not only do regulators operate in an environment of uncertainty, they also face conflicting incentives when trying to reduce the potential for errors in drug-approval decisions that might encourage them to be excessively cautious. Excessive caution can lead to the loss of potential health benefits from obtaining new medicines sooner. These losses are not obvious to the public but they are real nonetheless.

There are four underappreciated concepts that allow us to assess risk in a broader context. These four concepts complement the regulatory process by offering a greater degree of objectivity in determining whether a drug should or should not be available to patients and in minimizing the negative externalities associated with regulatory decisions. First is an evaluation of the *net risk* that a drug represents after accounting for its potential health benefits. Second is an assessment of the *alternative risk* that a drug represents relative to available therapeutic alternatives, including the possibility that there are no existing alternatives. Third is an assessment of the *universal risk* that a drug represents relative to the risk already accepted by the public in using many other types of regulated and non-regulated goods, services and activities—even those that are not directly comparable to drugs. Fourth is an assessment of the *identifiable risk*, or whether there are particular patient characteristics that make only certain people susceptible to the risk statistically associated with the drug's use. Applying these concepts to the assessment of drug risk might help speed up access to new medicines.

Studies have shown that faster drug approvals are not conclusively linked to higher rates of unsafe drugs entering the market. At the same time, there is evidence to suggest that slower approvals lead to a significant net loss of potential health benefits—a serious but hidden cost of increasing the level of regulation over drug safety. One way to reduce the loss of potential health benefits is to reassess the context in which we evaluate the safety of new medicines. Policy makers should focus on improving the efficiency of the current drug approval process and should consider the merit of empowering consumers with more choice over how to preserve and improve their own health.

Introduction

Health Canada recently posted on its website *The Progressive Licensing Framework: Concept Paper for Discussion* [Health Canada, 2007]. This paper proposed a new system of progressive drug licensing that would potentially fast-track pre-marketing approval of new medicines in exchange for greater post-marketing surveillance of drug safety. This proposal has the potential to speed up access to new medicines without sacrificing patients' safety if it is built upon sound principles of risk assessment. But the proposal will further reduce access to new medicines if it is pursued without an understanding for the broader context of risk or without an appreciation of the trade off between costs and benefits linked to excessive regulation of drug safety.

The purpose of the present publication is to contribute to the public dialogue about drug safety regulation and to raise the awareness of the general public about some important but perhaps underappreciated concepts about risk that should be part of the decision-making process when drug-safety standards are defined. I discuss the rationale for the regulatory review of drug safety and briefly examine problems related to uncertainty that affect regulatory standards and decisions about drug safety. In addition, both the obvious *and* hidden costs associated with regulatory efforts to minimize risk are addressed. The paper will also discuss four concepts I have labelled *net*, *alternative*, *universal* and *identifiable* risks. I explain how these ideas might help inform the decision-making process of drug-safety regulators. Finally, for discussion purposes, reference is made to a couple of interesting proposals for improving the process of granting marketing approval for new medicines in order to speed up access by patients to new medicines. The discussion and proposals are informed by the values of consumer empowerment and are concerned with maximizing patients' choice of treatment options.

Rationale for pre-market review of drug safety

Governments across the world regulate access to drugs on the basis of product safety because it is argued that the market fails to protect consumers adequately from potential health risks. For instance, Health Canada has a national mandate to ensure the safety of drugs sold in Canada and therefore regulates which products are allowed to be sold, and under what conditions. In order to obtain marketing approval for a new drug, manufacturers must provide Health Canada with evidence of its successful clinical testing in patients. After a lengthy and expensive clinical testing period, drug makers submit their applications for approval to Health Canada and then must wait for the regulator to issue a Notice of Compliance (NOC). The NOC certifies that the new drug meets all regulatory requirements for demonstrating that it is safe and effective for sale in Canada. After the NOC is issued, the new drug is legally allowed to be sold.

Ironically, regulatory safety review of new drugs is a time-consuming and imperfect process that comes at the cost of *promoting* public health. Delaying or denying access to important new medicines can negatively affect patients' health outcomes. Slower drug approvals can also produce other unintended outcomes. For instance, the longer a new drug is kept off the market while waiting for government's safety approval, the shorter is the effective period under which a drug can be sold with patent protection. [1] The resulting loss of profitable returns for the drug's inventor can negatively affect the capacity and incentives for developing new medicines [Vernon, 2005]. This, in turn, could conceivably harm future generations of patients. Therefore, it is important to examine the validity of the argument that market failure justifies government intervention through the regulatory approval of drug safety.

Part of the rationale used to justify pre-market regulation of drug safety is the contention that the market is not as effective as government regulators at reducing the potential harm that might be caused by unsafe drug products due to imperfect and asymmetric (or unequal) information between sellers (medicine producers) and buyers (patients) [Arrow, 1963]. Specifically, consumers face an information deficit about the qualities of new drugs that leaves them exposed to potential harm. At the same time, it is alleged that drug companies might have a profit incentive to carry out insufficient clinical testing, or overemphasize their product's benefits while downplaying its adverse effects. An additional assumption is that the information asymmetry facing consumers is not adequately mitigated by the presence of a physician acting as an expert agent. There is also an assumed absence of other market mechanisms—like non-governmental organizations that promote consumer product safety or publish various consumer reports—that could resolve this issue in the absence of government

[1] Patent protection is guaranteed for 20 years from the registered discovery of a new drug.

intervention. Therefore, it is reasoned that individuals cannot be left to use their own judgement when obtaining new medicines and a centralized government regulator should limit individual choice about the use of drugs to protect public health. The potential harm that can be caused by an unsafe drug rises to a level of seriousness that demands pre-emptive risk reduction strategies.

However, this criticism of the market is too extreme. Generally speaking, firms (especially drug companies given the seriousness of the consequences for human health) have a strong incentive not to misrepresent the safety of their products because doing so could damage their reputation in the market and ultimately destroy demand for their products altogether. Further, penalties for unethical corporate behaviour can be enforced through the legal system via tort and sometimes even criminal charges if harm comes to consumers from unsafe products.

Patients can also rely on the expertise of their physician to partially close the information gap about drug products. The requirement for consumers to obtain an expert opinion via an examination and prescription from a physician already makes the consumption of drugs uniquely more controlled than the consumption of other goods and services which could also be dangerous. The availability of expert agents that can be contracted to act on behalf of consumers is a way for the market to reduce information asymmetry.

The relationship between consumers and expert agents can be distorted if the expert has a conflicting financial interest in the advice given. For instance, if a physician were to receive a financial benefit from prescribing a given type of treatment, this could create a conflict of incentives between serving the interests of the patient, and gaining financially from prescribing something that might not necessarily benefit the patient. But again, expert agents face strong disincentives for unethical behaviour because their reputations can be damaged and they are also subject to tort and legal liabilities from malpractice, as well as penalties applied by their professional associations.

Uncertainty and imperfect information in regulatory decisions about drug safety

Approving a new drug requires regulators to make decisions with imperfect knowledge. There are significant limitations to the information that can be generated by pre-market clinical trials as well as post-market drug surveillance. Imperfect information leaves regulators in a position of uncertainty. Yet there are diminishing returns from increased drug testing designed to reduce uncertainty further. To make matters worse, not only do regulators operate in an environment of uncertainty, they also face conflicting incentives when trying to reduce the potential for errors in drug-approval decisions that might encourage them to be excessively cautious.

Limitations of clinical trials

Data obtained from clinical testing is not necessarily a reliable reflection of the expected effect of a drug in the general population. The results obtained from pre-marketing clinical trials for a new medicine sometimes do not reveal effects that later become apparent when the drug is used by a larger patient population. The safety of new agents cannot really be known with certainty until a drug has been on the market for many years [Lasser et al., 2002]. For example, a large clinical trial involving 5,000 patients might not reveal an adverse reaction that occurs at the rate of 1 in 10,000 patients. Participants in a clinical trial are required to be assessed against a number of inclusion and exclusion criteria necessary for the clinical assessment of the drug. These criteria might not completely reflect the characteristics of the broader population of patients. Additionally, to isolate the effect of one specific medication, patients in clinical trials usually do not receive other medications and do not suffer other known disease conditions [Lasagna, 1998]. This situation is hardly ever true for the patients who will take the drug after it is released to the market. This means that pre-release clinical trials may provide little insight into interactions and adverse reactions in populations with a number of medical conditions and prescriptions.

Limitations of post-market surveillance

There are also limitations to the use of data obtained from the post-market surveillance of a drug's effects on the general population. There is usually little agreement among clinical pharmacologists on what causes an adverse drug reaction. And a direct link

between a drug and the adverse reaction is almost impossible to establish with certainty. For patients who take several drugs at the same time, it is hard to isolate which drug or what combination of drugs caused the underlying reaction. Often the side effects caused by drugs do not have any uniquely attributable characteristics and anything that can be caused from a drug in an adverse reaction could also occur independently [Lasagna, 1998]. Furthermore, patients do not always receive prescribed drugs as directed and non-compliance can lead to harmful consequences for human health [Lasagna, 1998]. In fact, it is estimated that 30% to 50% of the adverse drug reactions are preventable because they result from over- or under-dosage and non-compliance [Sjoqvist, 2000].

In addition, from a statistical standpoint there is a high degree of variability in the rate of adverse drug reactions (ADRs) reported to health agencies. The change in the number of ADRs reported to health agencies is used to justify the withdrawal of a new drug from the market. However, the change in reported ADRs often represents only a single year of data and thus does not rule out the possibility that it was merely a result of statistical chance. Without the drug remaining on the market long enough to show a pattern, there is just no way to know if the number of reported ADRs might have returned to the previously observed lower rates (or even below them) in following years.

To illustrate this concept, table 1 compares the incidence of ADRs associated with the use of drugs that were withdrawn from the market because of safety concerns. The data for withdrawn drugs is compared to drug products in the same therapeutic class that have remained on the market. All of the withdrawn drugs in table 1 were voluntarily removed by the manufacturer except for *cisapride*, which was removed by Health Canada. In some cases (*cisapride* and *cerivistatin*) the year-to-year change in ADRs reported to Health Canada for withdrawn drugs increased dramatically in proportional terms. For example, in 2000, reports of ADRs that Health Canada classified as "suspected" of being associated with the use of *cisapride* increased nearly nine times from the rate in 1999. Similarly, in 2001, reports of ADRs associated with *cerivistatin* increased nearly five times from the year before. However, this does not appear to have been the case with *nefazodone*. The year-to-year change in ADRs for *nefazodone* does not appear to be as dramatic and, in absolute terms, is much lower than the other drugs that were withdrawn. Finally, the variability in the rate of ADRs per 100,000 prescriptions of *nefazodone* does not appear to be much different from an alternative drug in the same therapeutic class that remained available in the market. Without further years of data, it is simply impossible to know whether the observed results in any of these cases represented real risks or statistical anomalies.

Cost of increasing post-market surveillance

The cost of increasing post-market surveillance must also be considered. Post-market surveillance can be an important part of a drug's safety and efficacy assessment. It can corroborate the findings of previous clinical studies and add new information that

Table 1: Variability in the number of reports to Health Canada of "suspected" adverse drug reactions (ADRs) per 100,000 prescriptions dispensed, for prescription drugs withdrawn from the market and their therapeutic alternatives (only reports classified as serious), 1999 to 2003

Active ingredient (product)	Current status	Year	Total prescriptions dispensed	Total ADRs	ADRs per 100,000 prescriptions
Nefazodone (Serzone)	Withdrawn	1999	526,459.00	26	4.9
		2000	521,202.00	16	3.1
Venlafaxine (Effexor)	In the market	1999	543,720.00	29	5.3
		2000	1,107,061.00	30	2.7
		2001	1,878,399.00	47	2.5
		2002	2,746,453.00	77	2.8
		2003	3,723,402.00	134	3.6
Cisapride (Prepulsid)	Withdrawn	1999	1,052,914.00	16	1.5
		2000	383,135.00	51	13.3
Erythromycin (Stievamycin)	In the market	1999	429,870.00	13	3.0
		2000	346,666.00	8	2.3
		2001	298,176.00	10	3.4
Domperidone	In the market	2002	398,795.00	4	1.0
		2003	378,282.00	1	0.3
Cerivastatin (Baycol)	Withdrawn	2000	586,452.00	22	3.8
		2001	594,604.00	109	18.3
Lovastatin (Mevacor)	In the market	1999	497,121.00	6	1.2
		2000	447,941.00	12	2.7
		2001	398,036.00	4	1.0
		2002	316,344.00	2	0.6
Pravastatin (Pravachol)	In the market	1999	1,660,848.00	7	0.4
		2000	1,663,410.00	6	0.4
		2001	1,582,519.00	24	1.5
		2002	1,947,906.00	34	1.7
		2003	1,540,248.00	20	1.3
Simvastatin (Zocor)	In the market	1999	1,801,569.00	13	0.7
		2000	1,903,372.00	13	0.7
		2001	2,165,150.00	21	1.0
		2002	2,983,333.00	41	1.4
		2003	3,508,350.00	36	1.0
Fluvastatin (Lescol)	In the market	1999	338,392.00	5	1.5
Atorvastatin (Lipitor)	In the market	1999	2,627,018.00	35	1.3
		2000	3,870,518.00	53	1.4
		2001	5,370,407.00	135	2.5
		2002	7,046,361.00	227	3.2
		2003	8,548,624.00	154	1.8

Sources: Health Canada, Canadian Adverse Drug Reaction Information System (CADRIS), 2006; IMS Health Inc. Canada, 2004.

can only be obtained after the product has been used by the larger patient population [Lasser et al., 2002]. However, pre-market regulation of drug safety already involves a significant trade-off: assurance of product safety at the cost of lengthy delays before the health benefits associated with a new drug are available to patients. Increasing the rigour or scale of pre-market clinical testing would worsen this trade-off and add additional costs to drug development, which is already expensive. The significant cost of implementing post-market surveillance could also dramatically increase the cost of new drugs. If these costs cannot be passed on to consumers in the price of the drug, the resulting effect on drug makers would be to reduce their capacity and incentives for developing new medicines.

According to recent estimates, on average it takes US$802 million and more than ten years to develop a new medicine [Adams and Brantner, 2006; DiMasi et al., 2003]. A significant proportion of this expenditure is allocated to extensive clinical testing of the safety and efficacy of new drugs. This phase of testing consumes on average five to seven years of the drug-development period [Adams and Brantner, 2006; DiMasi et al. 2003]. The process of developing new medicines is also very risky. Only 1 in 10,000 compounds discovered are actually approved for sale [DiMasi, 2001]. The probability of a firm obtaining regulatory approval in the United States for new drugs that actually complete testing also remains low and is estimated to be about 20% [Adams and Brantner, 2003]. For those drugs that eventually reach the market, long approval times reduce the effective period of patent protection and therefore increase the amount of lost profit that would have been earned if market approval had happened earlier. In fact, only three in ten drugs approved will actually make enough money to recover the average development costs [Grabowski et al., 2002].

In economic terms, the additional information on drug safety and efficacy that can be obtained from more rigorous or frequent testing is subject to diminishing returns. In other words, the additional amount of reassurance of drug safety that comes with more testing gets smaller as more trials are conducted. At some point, both the direct and indirect costs of more testing outweigh the benefits that can be gained from it.

Unbalanced regulatory incentives from type-1 and type-2 errors

Imperfect knowledge can lead to errors in regulatory decisions. A drug-approval regulator can make two types of errors. The first decision error, commonly called type 1, is that of mistakenly allowing an unsafe drug into the market. A type-2 error is the opposite: mistakenly rejecting a new drug that is safe and effective [figure 1] [Grabowski and Vernon, 1983]. The regulator faces unbalanced incentives to reduce these two kinds of errors [Grabowski and Vernon, 1983].

Figure 1: Drug safety decision matrix

		new drug is safe and effective	new drug is not safe and effective
Regulator's decision	accept	correct decision	type-1 error
	reject	type-2 error	correct decision

Source: Koka and Skinner, 2006.

The burden of a type-2 error is borne directly by consumers, who suffer harm because they are denied access to a potentially beneficial treatment that they may have been willing to risk much earlier. Type-2 errors also directly affect drug makers. When a regulator mistakenly refuses to allow a new effective medicine to enter the market, the innovative drug firm loses the opportunity to earn the revenue that could have been gained from sales of the unapproved drug. The loss of revenue could affect decisions to invest in the development of new medicines in the future.

Conversely, regulators face very few potential negative outcomes from making a type-2 error. The lost health benefits caused by a regulator who mistakenly rejects a safe and effective drug are hidden from the public. The public never becomes aware of the lost potential health gains since the drug never becomes available on the market in the first place. By contrast a type-1 error is very obvious to the public. Adverse drug reactions are monitored and reported by health professionals and researchers, and vigorously publicized by the media. Type-1 errors, therefore, expose regulators to far greater public relations repercussions than type-2 errors.

The unbalanced incentives upon the regulator to avoid each type of decision error can lead to excessive caution in the approval process for drug products. Excessive caution minimizes the risk that the regulator will be held responsible for any errors but does not necessarily minimize the net health risk to the public as a whole that is caused by the loss of unrealized, potential health benefits.

Conceptual framework for defining drug safety

Current regulatory standards for drug safety are based on subjective thresholds for determining what constitutes an unacceptable level of risk from the use of a drug. Risk is measured through the use of randomized, controlled, clinical trials in which a relatively small test group of patients is exposed to a new drug and compared to a group that is not exposed to the new drug. The *absolute risk* is the actual rate of negative health effects that occur in the exposed and unexposed groups. When the absolute risk in the exposed group is stated in ratio to the occurrence of the same negative health conditions observed in the unexposed group it becomes a measure of *relative risk*. The *attributable risk* (i.e. the risk statistically associated with the use of the drug) is stated as the absolute risk observed in the exposed group minus the absolute risk observed in the unexposed group. After it has been determined that there is an attributable risk, the difference observed between the exposed and unexposed groups must be assessed to determine whether it is statistically significant or possibly just a result of random chance. Finally, once it has been determined that there is a statistically significant attributable risk associated with the use of a drug, then regulators must determine if the magnitude of that risk is sufficient to deny, delay, or modify marketing approval for a new drug product [Portney and Watkins, 2000]. [2]

Below I introduce four additional concepts [3] that enhance this conceptual framework and allow us to assess risk in a broader context. [4] These four concepts complement the present regulatory process by offering a greater degree of objectivity in determining whether a drug should or should not be available to patients and in

[2] It is also important that, when comparing risks, one also consider the difference between known and unknown risks. Obviously, pre-emptive actions to promote safety are appropriate when risks are known. By contrast, it might be considered excessively cautious when regulators attempt to protect the public from unknown risks.

[3] To my knowledge, these particular concepts have not previously been presented in a comprehensive discussion about drug risk. However, I will gratefully acknowledge any authors who have made published contributions in this area, if these are later discovered.

[4] Drug-safety assessment might also be considered in the context of the effect that our standards have on incentives to invest in drug research that could lead to future health benefits. Studies that have evaluated the effect of regulation on pharmaceutical R&D have found a negative impact of the stringency of government regulatory standards on the rate of new drug introductions and R&D spending [Wiggins, 1981]. These studies have shown that strict safety regulations and the resulting long approval times, adversely affect firms and their incentives to innovate new remedies for human illness. Excessively cautious safety standards can have the unintended effect of reducing research and development of new medicines. In turn, this could cause the loss of many potential health benefits.

minimizing the negative externalities [5] associated with regulatory decisions. First is an evaluation of the *net risk* that a drug represents after accounting for its potential health benefits. Second is an assessment of the *alternative risk* that a drug represents relative to available therapeutic alternatives, including the possibility that there are no existing alternatives. Third is an assessment of the *universal risk* that a drug represents relative to the risk already accepted by the public in using many other types of regulated and non-regulated goods, services and activities—even those that are not directly comparable to drugs. Fourth is an assessment of the *identifiable risk*, or whether there are particular patient characteristics that make only certain people susceptible to the risk statistically associated with the drug's use.

Net risk: Health risks of denying access to potentially beneficial treatment

A drug's risk cannot be assessed in isolation from its benefits. For instance, if clinical evidence showed that 10 in 1,000 patients showed an increased health risk statistically associated with the use of a particular drug, would this be unacceptable? If it were also known that the health conditions of 500 in 1,000 patients treated with the same drug improved, would the risk assessment change? The answer depends on the qualitative difference between the severity of the risks and the value of the benefits being weighed. Clearly, the risk statistically associated with the use of drugs can be very serious, sometimes including death. In some cases, preventing serious adverse events statistically associated with a drug affecting few people might be more important than capturing the benefits experienced by many people, if the benefits are not directly related to the prevention of equally serious health risks. For example, a pain reliever might bring comfort and relief to millions but this particular benefit might be less important than saving a small number of people from heart failure statistically associated with the use of a drug.

However, in general the benefits of new drugs far outweigh the risks. For instance, it has been estimated that the costs of government-imposed delays in giving safety approval to drugs in the United States were far greater than the benefits derived from avoiding the side effects of new drugs. Research indicates that between 1963 and 1970 drug-approval delays (driven by expectations about safety assurances) cost patients the equivalent of US$350 million to US$450 million in lost health benefits, in exchange for about $100 million worth of adverse events avoided [Peltzman, 1973, 1974]. A decade later, when the drug lag in the United States was at its longest, Dale Gieringer of Stanford

[5] "Negative externalities" is an economic term that refers to the unintended negative consequences often produced by public policies.

University examined the consequences for mortality of the FDA's drug-approval delays [Gieringer, 1985]. Examining new drugs introduced in the United States between 1950 and 1977, Gieringer concluded that new medicines were statistically associated with a reduction in mortality by somewhere between 50 to 102 lives per 100,000. Therefore, delaying these drugs by just one year cost 37,000 to 76,000 lives per decade in the American population. Applying this finding to the actual drug lag of between 8 and 19 months led to the conclusion that the ban cost between 21,000 and 210,000 American lives per decade. On the other hand, between 1950 and 1980, 11 drugs were not approved by the FDA that were statistically associated with over 100 deaths or serious adverse events in other global markets where they were approved. Because of this, the FDA was credited with saving an estimated 5,000 to 10,000 lives per decade during the period by preventing Americans from using these medicines. Therefore, on balance, the adverse health events prevented by the FDA were far outweighed by the equally important lost benefits of other medicines not approved during the period [Gieringer, 1985]. Therefore, safety standards that delay the availability of new drugs can result in net losses of health benefits despite the good intentions of regulators.

More recently, Professor Lichtenberg of Columbia University examined US data from 1960 to 1997. 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, 2002]. And, research has shown that the average annual number of drugs approved in Canada during the 10 years from 1992 through 2001 was 30 new drugs per year or four less than the United States [Rawson and Kaitin, 2003]. Based on this data, Graham [2005] calculated that had Canada approved the same number of drugs annually as the United States did, the higher number of approvals would have saved about 130,000 life-years annually.

Alternative risk: Health risks of existing treatments or from non-treatment with a drug

Of course the adverse events statistically associated with new drug products can be more serious relative to the benefits, thus making the potential risks weigh much heavier in any regulatory decision. Yet, while the use of medicines for treating illness and disease is sometimes statistically associated with a degree of risk, this risk must also be assessed against the degree of risk inherent in any alternative treatments that would have to be used in the absence of a new drug.

For instance, the public already accepts the risks associated with many common over-the-counter (OTC) drugs, which do not require a prescription and have been on the market for decades. One of these drugs is *ibuprofen*, a common pain reliever available over the counter without a prescription. Late in 2005, an expert panel at Health

Canada found that *ibuprofen* poses just as much risk as controversial painkillers like Vioxx® and Bextra®. Vioxx® and Bextra® were pulled from the market because of claims that the class of drugs know as Cox-2 inhibitors were linked to increased risk of heart failure. Both drugs were later re-approved for sale. The Health Canada panel compared Vioxx®, Celebrex®, and Bextra® to the risks of *ibuprofen*. The panel found that Cox-2 inhibitors present the same increased risk of cardiovascular disease as traditional painkillers (non-steroidal anti-inflammatory drugs or NSAIDs) including *ibuprofen*. This implies that Cox-2 inhibitors pose a level of risk that patients and the medical community have already deemed acceptable for many years. The panel of experts also found that the benefits of all these drugs outweighed their disadvantages, and that the risks of using them were extremely low for healthy people [Health Canada, 2005a].

Another recent example involved the withdrawal of Adderall XR®, a central-nervous-system stimulant used for the management of Attention Deficit Hyperactivity Disorder (ADHD). After one year in the Canadian market, the drug was recalled following evidence of 20 sudden deaths in the United States, among which were 14 children and 6 adults [Health Canada, 2005b]. In March 2005, the Pharmacy and Therapeutics Committee at Children's Hospital Boston reviewed the available data from the FDA to assess the risk statistically associated with receiving the medicine and concluded that, while there was good reason to be cautious in administering the drug to patients with a history of heart disease, Adderall XR® posed no additional risk compared to other drugs in the same therapeutic category. In particular, the adolescent population's risk of cardiac death was the same as the risk present in similar stimulants [Alexander et al., 2005]. The FDA decided not to withdraw the drug from the market and Health Canada eventually allowed Adderall XR® back in the Canadian market in August 2005. [6]

The risks associated with medical treatment with drugs might also be compared to the risks associated with alternative treatments like invasive surgery, which may or may not be worse. When drugs are substituted for such procedures, the relative risks must be weighed. Cases where medical (drug) therapy is used as an alternative to a number of invasive surgical procedures include, for example, lung volume reduction in severe emphysema [National Emphysema Treatment Trial Research Group, 2003], ectopic pregnancy [Galen, 2005], coronary artery bypass surgery [Gersh et al., 1985]. In the case of ectopic pregnancy (pregnancy located outside the uterine cavity), a life threatening condition if left untreated, the availability of a drug called *methotrexate* can substitute for surgery in 85% of the patients identified with the condition [Galen, 2005].

[6] This is not to say that, if a drug's risk profile is higher than that of another drug in the same therapeutic class, that it should be banned by government regulators. Some patients might tolerate one drug better than others. The reduction in side effects can encourage patients to stick to their treatment thus improving overall health benefits. Having more options available to patients theoretically makes it possible to satisfy the individualized health needs of consumers more completely.

Hypothetically, one can imagine a circumstance where the known risk of surgery might be higher than the known risk of using an alternative drug therapy.

The risk of using the new drug must also be weighed against the risk of not using it and leaving the underlying disease condition untreated. In other words, what is the alternative when a new drug is withdrawn? In many cases, withdrawing a drug may leave no alternatives and this might carry its own risks. Consider a hypothetical illustration where the percentage of patients dying from a diagnosis of a particular form of cancer if untreated is 50% and a new drug has been shown to reduce the probability of dying from the disease to 45% of patients treated. Assume also that the observed mortality from adverse reactions linked to the use of the new drug occurs in less than 1% of patients treated. Under this scenario, taking the drug raises the risk of death by approximately 1%, but not taking the drug raises the risk of death even more, by approximately 5%. [7]

One example of this concept is the case of the drug Lotronex®, which treated serious forms of intestinal and bowel disorders. It was withdrawn from the US market in 2000 for safety concerns. By the time the drug was withdrawn, the FDA had received reports of 70 cases of a serious post-marketing adverse event, including 49 cases of ischemic colitis and 21 cases of severe constipation. Of the 70 cases, 34 resulted in hospitalization, 10 resulted in surgery, and three resulted in death. However, it is estimated that 150,000 patients had used the drug [CNN & AP, 2000]. Therefore, 149,930 people had used the drug without any reported difficulties. This makes the overall rate of adverse reports about 1 in every 2,143 patients. Hospitalizations occurred in about 1 in every 4,412 patients, surgeries at the rate of 1 in 15,000, and deaths at the rate of 1 in 50,000. After its recall, thousands of people who had been taking Lotronex® lobbied the FDA for renewed access to the drug because at the time it was the only drug on the market to treat serious forms of intestinal and bowel disorders. In other words, without Lotronex® 149,930 people would have suffered from the adverse conditions associated with serious intestinal and bowel disorders. In 2002, the FDA finally again allowed patients access to Lotronex®—but only on a highly restricted basis.

Universal risk

The risk statistically associated with the use of any drug must also be considered in the context of the already accepted risk statistically associated with the use of non-medical products in general. The public is allowed access to products that are associated with known significant health risks (e.g. tobacco, alcohol) yet offer no counter-balancing

[7] This could also be interpreted as a net benefit of a 4% reduction in mortality associated with the use of the new drug.

health benefits. How can we justify a higher standard for safety expectations if those standards prevent or significantly delay access to new medicines with both measurable risks and benefits? Access to new drugs is also dependent on the approval of a physician as an authorized prescriber. This is already a much higher standard of consumer protection than applied to non-medical products associated with a demonstrably higher risk of causing adverse health conditions.

Assessing whether the risk associated with drugs is acceptable should depend at least partially on a comparison of the risk accepted from less-regulated consumption goods. We are constantly exposed to risk in our daily lives even through the most mundane activities and we actually accept significant risk regularly. In many instances, the risks associated with these activities are significant and yet we do not see governments banning any of these activities in the way they ban drugs that affect much smaller percentages of the population.

For example, according to a report by the US Center for Disease Control, 47% (138 million) [8] of Americans could be classified as current regular drinkers in 2004. The data show that the number of alcohol-induced deaths, excluding accidents and homicides, was 20,687. The number of deaths caused by alcoholic liver disease alone was 12,360. Therefore, the overall risk of mortality associated with the use of alcohol occurred at a rate of approximately 1 in every 6,671 (or 150 per 1,000,000) users. The risk of death from liver disease alone occurred at the rate of 1 in every 11,165 (or 90 per 1,000,000) users. These figures do not even account for the less serious health conditions affected by alcohol use in the United States. While the number of doses of alcohol required to produce such statistics is different than that required by some prescription medications, in this context, the adverse health risks statistically associated with the use of new medicines do not appear to justify extreme precaution, especially when one considers that new medicines also represent real health benefits for large numbers of people.

Identifiable risk

When a risk is found to be statistically associated with the use of a drug, it is still incumbent on researchers to ask whether there are particular patient characteristics that are statistically associated with the risk so that a warning can be added to the product monograph. If the patient group at a higher risk from a specific drug can be detected, a drug can still be approved for those who face lower risks and the potential loss of health benefits reduced.

[8] US Bureau of the Census reports that the estimated population of the United States was 293,638,158 as of July 1, 2004 [US Census Bureau, 2006].

Vioxx® (*rofecoxib*), mentioned earlier, is also a good example of the application of identifiable risk. 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). Subsequent research suggested that Vioxx® increased the risk of cardiovascular problems such as heart attack and stroke. However, even though there was an observed increase in association of heart attack or stroke and the use of Vioxx®, this does not automatically mean that the government should not approve it for sale. For instance, an estimated 15,000 Americans die each year from gastrointestinal complications statistically associated with the use NSAIDs [Gilmartin, 2004]. A well-informed patient, at low risk for a heart attack or stroke but high risk of GI complications from other NSAIDs, might choose Vioxx®. Many patients with such a risk profile might willingly choose the increased cardiovascular risk of Vioxx®, given its other benefits in reducing the sometimes equally serious side effects statistically associated with the use of NSAIDs.

For another example, phenylpropanolamine (PPA), an ingredient that was used in cold, cough, allergy as well as weight-loss (i.e. appetite-suppressing) medicines, was withdrawn in Canada in May 2001 (it was also withdrawn in the United States). According the advisory issued by Health Canada, the withdrawal followed a study from Yale University that established a link between PPA and hemorrhagic stroke occurring mainly in women. An updated study published in *CMAJ* indicated that the risk was highest among ethnically African women who smoked cigarettes and suffered from hypertension [De Foa, 2002]. Another advisory published by Health Canada in November 2000 indicated that in the last 20 years only one report of hemorrhagic stroke due to the consumption of PPA was recorded in the Canadian Adverse Drug Reaction Monitoring Programme. In the United States, 60 similar cases were reported since the ingredient first became part of several cold remedies in 1969 (2 strokes per year). Meanwhile, each year millions of patients in both countries have consumed drugs containing PPA and enjoyed the benefits and relief statistically associated with the medications. Only a minority of these patients belong in the high-risk group identified as being in danger of a hemorrhagic stroke [De Foa, 2002].

Another example is the drug *cisapride* referred to earlier. Following 44 reports of serious cardiac arrhythmias for about a decade, out of which 10 resulted in sudden death, Health Canada withdrew *cisapride* from Canadian pharmacies in May 2000. The evidence from the FDA included 261 adverse reaction reports in the United States with cardiac abnormalities and 80 deaths at the time of withdrawal. *Cisapride* is a drug used for the treatment of gastroparesis, intestinal pseudo-obstruction, and gastroesophageal reflux disease [Health Canada, 2000]. As with other drugs, the factors that placed patients using *cisapride* at risk for cardiac-rhythm adverse events were possible to identify [De Foa, 2002]. Currently, patients can still obtain the drug through

the Special Access Program only if their physician determines that treatment with *cisapride* provides benefits that are sufficiently large to outweigh the risk of potential heart complications.

Banning a drug for everyone on the basis of a revealed risk among some patients, instead of identifying the specific risk characteristics associated with an adverse reaction jeopardizes potential future health gains in other ways. Even drugs known to be dangerous under some circumstances might have great benefits when used to treat entirely different health conditions. For example, during the 1950s and 1960s, the use of *thalidomide* as a tranquilizer for pregnant women became associated with severe birth defects. Experimental samples of the drug were distributed to physicians in both Canada and the United States for about two years, leading to the approval of *thalidomide* in Canada in 1961 [Warren, 1999]. As many as 125 victims of *thalidomide* are identified from the Thalidomide Victims Association of Canada. In the United States, *thalidomide* was never licensed and the exact number of victims is not known with accuracy. Some estimates indicate that around 20,000 patients received the drug in the United States and about 17 babies were born with birth anomalies. Some have estimated the number of cases of birth defects worldwide might have reached as high as 8,000 [Scherer, 2001]. *Thalidomide* was eventually withdrawn from worldwide pharmaceutical markets. Yet, in 1998 the FDA approved *thalidomide* for the treatment of leprosy, and other "off-label" [9] uses are becoming increasingly popular. In particular, the drug is used as a treatment for blood cancer, AIDS, and multiple myeloma (bone marrow cancer). Health Canada also now allows the use of this drug by a limited number of patients under the Special Access Program.

If the risk characteristics of patients that are associated with adverse reactions linked to the use of a drug can be identified, then a drug can still be safely released to the market with warnings and labels to reduce the risk to particular patients without giving up the potential health benefits for everyone else.

[9] "Off-label" refers to the prescribing of a drug for health conditions that were not considered during the original approval process.

Policy discussion

Health Canada as a certifier, not a gatekeeper

In 2005, John R. Graham published a paper in which he argued that one option for speeding up access to new medicines is to move from a system where the government grants legal permission to sell a new drug to one where it simply certifies the safety and effectiveness of new drug products after they are on the market [Graham, 2005]. If the current regulatory mandate was changed in this manner, drug products would be marketed immediately after their development and Health Canada would then assess the safety and effectiveness of drugs and publish a certification for products that pass government standards.

According to Graham [2005], this option derives from actual practice in other areas of consumer risk. One example is Underwriters' Laboratories (UL), which has certified products since 1894 as an independent, non-profit, organization. Underwriters' Laboratories 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]. Another well-known example is the Canadian Standards Association (CSA). The Canadian Standards Association is a private-sector, not-for-profit, membership-based association serving business, industry, government, and consumers in Canada and the global marketplace. CSA develops standards that enhance public safety and health for a wide range of consumer products [CSA, 2007].

If this approach were adopted, Health Canada would largely return to its earlier role of ensuring that products are not misbranded or adulterated [Miller, 2000]. Changing Health Canada's mandate from drug approval to drug certification has the advantage of allowing Canadians who prefer to accept more risk with their medicines to act earlier, on 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 thorough testing [Graham, 2005].

According to Graham's proposal, Health Canada could 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. Health Canada could also certify new medicines according to its own time-frame. If manufacturers thought it valuable to have Health Canada remove its warning label, they could pay a user fee to have the department prioritize the review of their drug. Health Canada could also distribute 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. Health Canada could also communicate its warnings to the general public via its website, publications, or advertisements [Graham, 2005].

Harmonization, cooperation and reciprocity with regulators in other countries

A less radical approach to speeding up patient access to new medicines would involve cooperation and sharing of resorces with other national drug-safety regulators within the current regulatory framework. Graham [2005] has also suggested a cooperative system of harmonization, cooperation, and reciprocity in the approval of new medicines between Canada and other nations. Health Canada could speed up its regulatory process by taking advantage of the regulatory knowledge and capacity of other jurisdictions, rather than attempting to duplicate the American process for every drug brought to market. A consolidation of resources through the sharing of data, workload, and processes would be of great benefit. For example, if Canada entered into agreements of "mutual recognition" with other countries, new medications already approved in those countries could be introduced to the Canadian market far more rapidly and at lesser cost to the Canadian taxpayer. This concept has also been recommended by a government committee. In an effort to reduce the time taken to review new medications, Canada's recent Smart Regulation strategy proposed a form of mutual recognition to reduce persistent delays in the drug approval process [EACSR, 2004].

Will quicker access to new drugs raise the probability of harm?

There are legitimate concerns that allowing drugs to go to market sooner might compromise the safety of patients using new drugs [Lexchin, 2005]. Attempts have been made to test whether faster approval rates actually result in the increased marketing of unsafe drugs. Olson [2002] for instance found that faster approval rates of novel drugs are statistically associated with higher rates of adverse drug reactions. Using data on adverse reactions reported to the FDA's Spontaneous Reporting System and after controlling for drug and patient characteristics, the author estimated a negative and significant relationship between adverse events attributed to new drugs and the review time spent before their market approval.

Abraham and Davis [2005] assessed both regulatory processes and outcomes in the United Kingdom and the United States for the period from 1971 to 1992 (i.e. before the implementation of the Prescription Drugs User Fee Acts discussed below). An estimation of the drug safety withdrawals indicated that there were twice as many new drugs recalled from the market in the United Kingdom than in the United States. Several hypotheses were examined as to what was the main reason for the discrepancy in the regulation process between the two countries. The study concluded that the FDA set more stringent standards, which in turn required longer times to approve "safer" drugs to enter the market.

In 1992, the Food and Drug Administration in the United States introduced the Prescription Drugs User Fee Acts (PDUFA), a program that was designed to expedite new drug application review times. Health Canada quickly followed and introduced a similar program in 1995 [Graham, 2005]. In exchange for a lump-sum fee, these agencies are obliged to start immediate reviewing of the new application even though a faster approval is not guaranteed to the manufacturer. However, the user fee is tied to explicit performance measures in the United States, where the reduction in review times was quite remarkable, from an average of 28.2 months for the period from 1986 to 1992 to 16.1 months for the period from 1997 to 2002 [Berndt et al., 2005]. Explicit performance measures do not apply to Health Canada, which fell short of the success seen in the United States: it has yet to meet its 355-days target for a new drug approval. The introduction of the PDUFA in the United States offers an opportunity to measure the impact of faster approval times upon drug safety empirically.

Berndt et al. [2005] and Friedman [1999] analyzed trends of market withdrawals of drugs approved before and after the introduction of user fees in the United States and found no significant changes in the safety record of the FDA despite the reduction in approval times. Similarly, the US government's auditor reported 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 of the withdrawn drugs 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].

Another report by a non-partisan, US government agency, the Office of the Inspector General of the Department of Health and Human Services found similar results [table 2]. The analysis showed the withdrawal rate according to both the calendar and fiscal years in which the manufacturers applied to have the ban on their new drugs lifted. Although the rate increased a little bit in the five years after PDUFA, it dropped again the next half decade. This analysis strongly suggests that quicker access to new medicines in the United States did not raise the risk of harm from unsafe medicines.

Table 2: Rate of new molecular entities (NMEs) withdrawn from US market, before and after the implementation of the PDUFA in 1992, by five-year period.

	1983–1987	1988–1992	1993–1997	1998–2002
NMEs withdrawn as a percentage of total approved during the calendar years in period	3.7%	2.5%	3.6%	1.7%
NMEs withdrawn as a percentage of total approved during the fiscal year in period	2.7%	2.6%	3.1%	2.3%

Source: Rehnquist, 2003 (reproduced from Graham, 2005).

Conclusion

The purpose of this paper was to contribute to the public discussion surrounding the issue of drug safety standards and expectations, in response to a proposal posted on Health Canada's website. The proposal suggested fast-tracking pre-market drug approval in exchange for greater post-market surveillance of adverse drug reactions. The ideas and evidence discussed in this paper suggest that such a proposal is worthy of further positive consideration if it leads to quicker patient access to new medicines.

Studies have shown that faster drug approvals are not conclusively linked to higher rates of unsafe drugs entering the market. At the same time, there is evidence to suggest that slower approvals lead to a significant loss of potential health benefits. One way to reduce the loss of potential health benefits is to reassess the context in which we evaluate the safety of new medicines. This paper has drawn attention to four under-appreciated concepts for evaluating drug risks. These four concepts complement the regulatory process by offering a greater degree of objectivity in determining whether a drug should or should not be available to patients and in minimizing the negative externalities associated with regulatory decisions. First is an evaluation of the net risk that a drug represents after accounting for its potential health benefits. Second is an assessment of the alternative risk that a drug represents relative to available therapeutic alternatives, including the possibility that there are no existing alternatives. Third is an assessment of the universal risk that a drug represents relative to the risk already accepted by the public in using many other types of regulated and non-regulated goods, services and activities—even those that are not directly comparable to drugs. Fourth is an assessment of the identifiable risk, or whether there are particular patient characteristics that make only certain people susceptible to the risk statistically associated with the drug's use. Applying these concepts to the assessment of drug risk might help to speed up access to new medicines.

The proposals discussed in this paper should be interpreted from a perspective of making the current drug approval process more efficient and also empowering consumers with more choice over how to preserve and improve their own health. It is hoped that the ideas and evidence presented in this paper will be useful to policy-makers who are searching for ways to improve access to new medicines in Canada.

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