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Drug Safety and Health Canada

Going, Going...Gone?

By Joel Lexchin

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Executive summary

Drug safety is a serious issue and is increasing in prominence. In Canada 3–4% of drugs approved will eventually be withdrawn from the market because of safety issues, but the number of people exposed to these drugs is increasing because of aggressive marketing tactics by the pharmaceutical industry.

The Food and Drugs Act and its regulations theoretically give Health Canada considerable authority in dealing with safety issues, but there are also significant limitations in the legislation. Although the organization can cancel the market authorization for drugs without prior negotiations with companies, it cannot force them to recall drugs deemed harmful from pharmacy shelves. Health Canada can issue a public warning about a drug without the agreement of the company involved, but it cannot directly compel the company to revise the label of its product to reflect new safety information.

The priorities of Health Canada are skewed in favour of rapid approval of new drugs at the expense of the post-marketing pharmaco-surveillance system as judged by how money and personnel are allocated to each activity.

Faster approval of new drugs has the potential to produce more safety problems once drugs are on the market, especially since Health Canada faces financial penalties if it exceeds targets for the length of time that products spend in the approval process.

Although Health Canada has committed itself to defined standards with regard to drug approval times, it has explicitly rejected developing quantitative standards for evaluating its post-marketing pharmaco-surveillance system. In addition to lacking standards in this area, it has not made clear what its criteria are in issuing risk communication documents, and it does not monitor whether or not those communications have had the desired effect in terms of changing the way that drugs are prescribed and used.

Adverse drug reactions (ADRs), even serious ones, are significantly under-reported, but mandatory reporting does not seem to improve reporting rates in countries where it has been implemented. New Zealand has the highest rate of reporting of ADRs in the world, due to a variety of methods, including the feedback that it provides to individuals filing reports and outreach strategies to emphasize the importance of

reporting ADRs. Many of the features that the New Zealand system uses are ignored or inadequately implemented in Canada.

Wide dissemination of safety information is necessary to allow practitioners to prescribe appropriately, and for consumers to use drugs wisely. Health Canada, however, continues to treat all such data that companies submit in order to get a new drug approved as confidential business information that will not be publicly released without the consent of the company owning the data. What safety information it does release is insufficient to allow an adequate independent assessment of a drug's safety.

Progressive licensing is a new regulatory model that Health Canada is proposing to introduce that would allow it to retain regulatory control over a drug throughout the product's entire lifecycle, instead of effectively losing control once the product is marketed, as is now the case. However, in its initial incarnation in the form of Bill C-51, progressive licensing would have actually further strengthened Health Canada's reliance on the industry for information and would have worked to enhance regulatory secrecy.

Canada's post-marketing pharmaco-surveillance system could be significantly improved through a series of reforms undertaken by Health Canada, including:

- Health Canada should utilize the powers that it is given through the Food and Drugs Act to protect people's health rather than delay action through negotiations with drug companies.
- Health Canada needs to reorient its priorities so that post-marketing pharmaco-surveillance is on an equal footing with the approval of new drugs.
- Health Canada needs to devote significantly more resources to its post-marketing pharmaco-surveillance system.
- Health Canada should undertake a systematic study to examine whether faster drug approvals lead to more post-marketing safety issues.
- Health Canada needs to develop measurable standards to judge its post-marketing pharmaco-surveillance system.
- Health Canada needs to publicly and transparently explain what criteria it uses in issuing safety communications.
- Health Canada needs to systematically analyze whether its methods of communicating with health care professionals and the public are producing the desired effects.
- Health Canada should study the methods that New Zealand uses in its post-marketing ADR system and adapt them for Canadian use.
- Health Canada needs to stop treating safety information as confidential and commit to making all safety information publicly available promptly after approving a new drug.
- Health Canada should use progressive licensing in order to decrease its dependence on industry for information by ensuring that post-marketing studies are undertaken, analyzed, and reported on, independent of industry. Furthermore, progressive licensing should enhance the transparency of safety information rather than further secrecy.

Drug Safety and Health Canada: Going, Going...Gone?

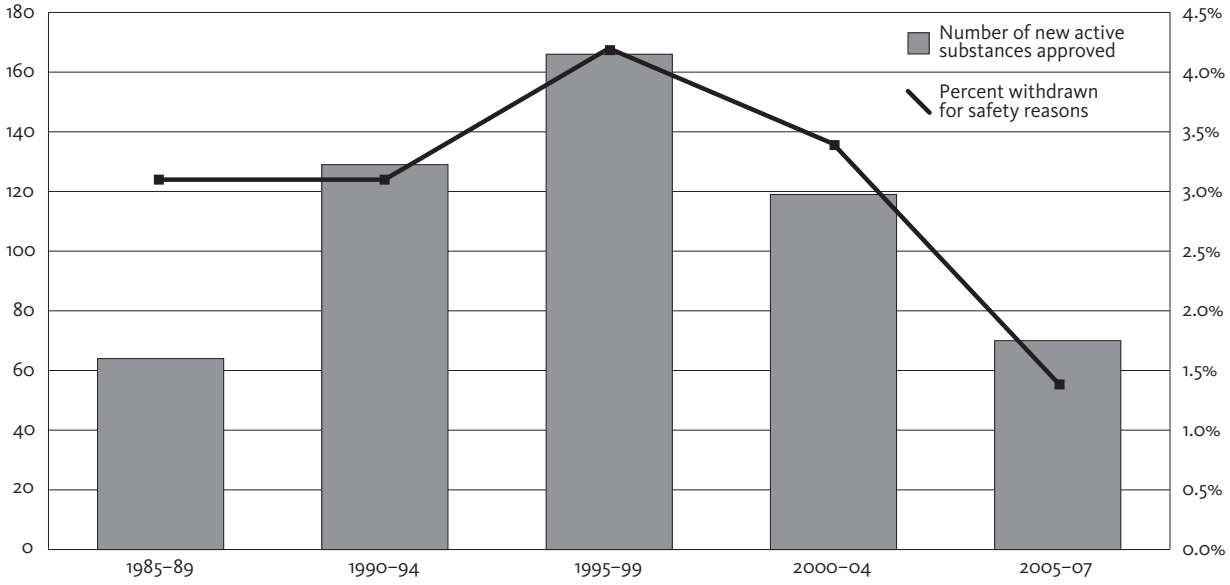
Evaluating the safety of prescription drugs prior to approval and monitoring their safety once they have been marketed should be a major priority in any drug regulatory system. In the United States (U.S.), adverse drug reactions (ADRs) are the 4th to 6th leading cause of death, contributing to more than 100,000 deaths and 1.5 million hospitalizations yearly.[1] Since that estimate was made in the late 1990s, the severity of the problem has only heightened with a marked increase in reported deaths and serious injuries associated with drug therapy.[2] Although these figures come from the U.S., there is no reason to believe that the situation is any different in Canada.

Over the past two decades, about 3-to-4% of the drugs approved by Health Canada subsequently needed to be withdrawn from the market for safety reasons (*see Figure 1*).[3–5] Although the percentage of withdrawals has remained relatively stable, aggressive marketing of new drugs by companies means that an increasing number of people are exposed to these products before they are removed from the market. In the two to four years,that bromfenac, dexfenfluramine, and mibefradil were on the U.S. market in the mid- to late 1990s, 6.4 million people were exposed to them.[6] Two of the five most heavily promoted drugs in Canada in 2000 (Baycol and Vioxx) were subsequently withdrawn because of safety issues. Furthermore, Table 1[3, 4] shows that even drugs that have been on the market for many years cannot be regarded as safe. Sometimes safety problems are not recognized for decades.

This report starts by looking at the powers that the Food and Drugs Act and its Regulations give to Health Canada and the limitations in those powers, and then moves on to examine the emerging ideology behind how Health Canada sets its priorities in terms of approving new drugs and monitoring the safety of existing ones. The report then looks specifically at the allocation of resources between the Therapeutic Products Directorate (TPD), the arm of Health Canada charged with approving new prescription drugs, and the Marketed Health Products Directorate (MHPD), the part of the organization that monitors the safety of drugs already on the market.

The third section deals with how long it takes to approve new drugs. The time taken to approve new drugs has been dropping in the past decade, and approval times have taken on added impor-

FIGURE 1 **Safety withdrawals as a percent of approvals, 1985–2007**



tance because whether or not target times for considering drugs are met influences the amount of money that the TPD will get in user fees from drug companies. Both of these issues related to approval times may impact on safety.

The fourth section points out the contradiction between Health Canada setting measurable standards in the drug approval process while explicitly declining to do so when it comes to safety. Decision-making around if, and when, to issue safety warnings about drugs and when to pull them from the market and how Health Canada fails to monitor the effects of its safety warnings is discussed in the fifth section. The sixth part of this report notes that ADR reporting is one of the key components of a post-marketing drug safety system, but, compared to the best systems in the world, the one used by Health Canada has serious deficiencies.

The seventh section looks at the availability of safety data. Health Canada regards all information, including that on safety, that is submitted by pharmaceutical companies as part of the drug approval process as confidential business information and will not release it without the express consent of the company. This level of secrecy, combined with a lack of safety information in published clinical trials, means that health care practitioners are ill-informed as to the risk-benefit ratio of new drugs. The information that Health Canada does release in the form of the Summary Basis of Decision is not sufficient to allow outside researchers to independently assess drug safety.

The penultimate section examines the emerging concept of progressive licensing and looks at its potential to enhance drug safety in Canada, and the report concludes by offering a set of recommendations for correcting the problems that have been identified.

Health Canada and the Food and Drugs Act

The Food and Drugs Act and its regulations theoretically give Health Canada considerable authority in dealing with safety issues, but there are also significant limitations in the legislation. Health Canada, acting on behalf of the Minister of Health, does not have to engage in any con-

TABLE 1 **Drugs withdrawn from the Canadian market since August 2004**

Drug		Approval date/ date of first listing in Compendium of Pharmaceuticals and Specialties	Date and main message in safety warning(s)	Date and reason for withdrawal
Generic name	**Brand name**			
Aprotinin	**Trasylol**	October 3, 1995		*November 23, 2007* Increase in all-cause mortality
Estradiol dienanthate /estradiol benzoate and testosterone enanthate	**Climacteron**	1961		*October 22, 2005* Endometrial hyperplasia/ carcinoma possible because appropriate progestin regimen unknown
Gatifloxacin	**Tequin**	January 9, 2001	*December 19, 2005* Serious cases of hyper and hypoglycemia have been reported. Careful monitoring of blood glucose is necessary when used in diabetic patients *February 16, 2006* Diabetic patients should not use *May 12, 2006* Contraindicated in diabetic patients and a boxed warning has been added to the product monograph dealing with disorders of glucose metabolism	*June 29, 2006* Serious disorders of glucose metabolism (nothing posted on Health Canada web site concerning withdrawal)
Lumiracoxib	**Prexige**	November 2, 2006	*August 16, 2007* Withdrawn in Australia due to serious liver problems	*October 3, 2007* Risk of serious hepatotoxicity cannot be safely and effectively managed
Pergolide	**Permax**	1991		*August 30, 2007* Valvulopathy
Rofecoxib	**Vioxx**	October 25, 1999	*April 19, 2002* Serious stomach problems can arise. Patients with a history of hypertension, ischemic heart disease or heart failure should talk to their doctor before using the drug	*September 30, 2004* Increased relative risk for confirmed cardiovascular events, such as heart attack and stroke
Tegaserod	**Zelnorm**	March 12, 2002		*March 30, 2007* Increase in cardiovascular ischemic events
Thioridazine	**Mellaril**	1959		*September 30, 2005* Cardiac dysrhythmias
Valdecoxib	**Bextra**	December 11, 2002	*December 2002* Rare cases of serious skin reactions *December 10, 2004* Should be used with caution in patients with, or at risk for, cardiovascular disease. A boxed warning regarding serious skin reactions has being added	*April 7, 2005* Life threatening skin reactions

sultations with a company before ordering the withdrawal of a drug because of safety concerns. However, the only recent situation where this power was actually exercised concerned Adderall XR™, a product used in treating attention deficit hyperactivity disorder in children.[7] (Adderall XR™ was subsequently allowed back on the market.) In all other situations, Health Canada has preferred to negotiate with drug companies prior to removing drugs from sale.

Negotiating instead of acting can have tragic consequences. Companies are often extremely reluctant to lose products, especially if they are ones that are generating large sales revenue. In the U.S., instead of withdrawing the anti-diabetic drug troglitazone (Rezulin™) from the market as the British did, the FDA and Warner-Lambert, the company marketing the drug, went through a protracted series of negotiations over a period of 29 months that resulted in four labelling changes to the information about troglitazone. By the time the drug was finally withdrawn, there had been more than 60 deaths due to liver failure. Had the FDA acted when the British did, there would have been less than half a dozen deaths. Over the time when the drug was sold, Warner-Lambert made $2.1 billion.[8] (Troglitazone was approved in Canada but never marketed because the company and the Patented Medicine Prices Review Board could not reach an agreement about the pricing of the drug.)

One example of the limitations in the Food and Drugs Act is that, although Health Canada can request that the responsible company recall a product that has been deemed harmful, it does not actually have the authority to make the company do so. Health Canada can issue a public warning about a drug without the agreement of the company involved, but it cannot directly compel the company to revise the label of its product to reflect new safety information. However, Health Canada can compel such changes by explaining to the manufacturer that without adequate changes the authority to initiate a stop-sale process will be invoked. Whether or not Health Canada has ever needed to invoke this threat in order to get the company to change labelling is not known.

While these are serious deficiencies in Health Canada's powers, the most significant limitation is that, once a drug is on the market, it cannot require the manufacturer to undertake any new studies into the product's safety. It can request this type of study, but experience in the U.S. indicates that many of them may never be done. In that country, between 2002 and 2005, a total of 743 unique postmarketing commitments were made by companies. By the end of 2007,just over a third were completed, 91 were delayed, and 200 had not yet started.[9] (Some of the 200 that were pending were not considered delayed since they had not yet passed the original projected beginning date, but an unspecified number also did not have FDA-imposed deadlines.) Companies are also required to submit annual reports to the FDA documenting the status of their commitments, but 35% of the 336 reports that were or should have been filed in 2004 were missing entirely or contained no useful information on post-marketing commitments, and 39% were missing one or more items of required informat

Health Canada's priorities

Over the past decade, financing for the TPD has shifted from coming entirely from government appropriations to, at one point, drug companies providing 70% of funding, and now about one-third comes from that source.[11] This shift in financing of the regulatory body has raised concerns about whether the TPD's primary commitment is still to public health.

An indication of a possible reorientation of the TPD in favour of business interests is reflected in its Business Transformation Strategy (BTS) that is in the process of being implemented. The BTS was introduced in early 2003 and "builds on the commitments made by the Government of Can-

TABLE 2 **Allocation of $40 million dollars for improvements in drug regulatory system, fiscal 2003–04**

Program area	Percent of money	Dollars ($ 000,000)
Improved regulatory performance	78	31.2
Enhanced post-marketing safety	6.5	2.6
Optimal drug therapy	6	2.4
Price review capacity	1.25	0.5
Therapeutic access strategy	8.25	3.3

TABLE 3 **Relative funding of TPD and MHPD, 2004**

Directorate	Approximate annual operating cost base (year ended March 31, 2004)	Approximate number of employees (as at March 31, 2004)
Therapeutic Products Directorate	$38 million	423
Biologics and Genetic Therapies Directorate	$22 million	228
Health Products and Food Branch Inspectorate	$16 million	190
Marketed Health Products Directorate	$8 million	90
Total	$84 million	931

ada to 'speed up the regulatory process for drug approvals,' to move forward with a smart regulations strategy to accelerate reforms in key areas to promote health and sustainability, to contribute to innovation and economic growth, and to reduce the administrative burden on business."[12]

One of the key phrases in the BTS is "smart regulation." Smart regulation means that Canada should "regulate in a way that enhances the climate for investment and trust in the markets" and "accelerate reforms in key areas to promote health and sustainability, to contribute to innovation and economic growth, and to reduce the administrative burden on business."[13] While health is not ignored, the emphasis is clearly on creating a business-friendly environment. The federal External Advisory Committee on Smart Regulation explicitly states that risk management has an essential role in building public trust and business confidence in the Canadian market and regulatory system.[14]

When applied to drug regulation, risk management means weighing potential negative effects against potential advantages. Potential negative effects are adverse health effects that might occur under reasonably foreseeable conditions.[15] The shift from the precautionary principle to risk management is subtle but unmistakable. The precautionary principle says that, if products cannot be shown to be safe, then they should not be marketed; risk management allows products on the market unless they are shown to be harmful. Realigning regulation to conform to the principles of Smart Regulation would not totally abandon the concept of precaution, but it seems to imply that there would have to be a threat of serious or irreversible damage before it would come into play.

The TPD is devoting significant organizational resources towards the goal of further speeding up the drug approval process. In the Budget speech outlining government spending for the 2003 session of Parliament, $190 million was allocated over a five-year period mostly to improving "the timeliness of Health Canada's regulatory processes with respect to human drugs."[13] Forty million out of the $190 million was appropriated for fiscal 2003–04. Out of that amount, 78% ($31.2 million) went toward "improved regulatory performance," mainly an effort to eliminate the

backlog in drug approvals and to ensure timeliness in getting drugs onto the market.[16] (Table 2)

This allocation of funds was made despite the fact that in 2004 the TPD was already much more heavily resourced than the MHPD (Table 3)[17] and as a result the MHPD had to stop routinely trying to assign causality when evaluating ADR reports. Information from each ADR report that is received is entered into a number of fields in the Canadian Adverse Drug Reaction Information System (CADRIS) database. Because of increased workload and funding constraints, the number of essential fields in the CADRIS database has been reduced, such that the "causality" field is no longer being systematically used. Two years later, in 2006, the allocation of personnel and money between the TPD and the MHPD had only marginally improved; although the MHPD now had 120 staff and a budget of $13 million, the comparable figures for the TPD were 525 employees and $42 million.[18]

In the summer of 2008, Health Canada announced it was allocating $1 million to an independent research network to study the safety of prescription drugs taken by Canadians. This was followed up in January 2009 with an additional $31 million over four years, and $10 million per year after that. This investment is a much stronger commitment than Health Canada has previously made to drug safety, but still falls short of the $20 million annually that a network of independent academics had estimated it needs.[19]

Faster drug approvals and drug safety

Health Canada has committed itself to a maximum of 300 days for deciding whether or not to approve non-priority drugs (180 days for priority drugs), and has devoted substantial resources to achieving this goal, as was noted in the previous section. Whether or not faster drug approvals result in a greater percentage of unsafe drugs reaching the market is the subject of an ongoing debate. Abraham compared drug withdrawals in the United Kingdom (U.K.) and the U.S. in the period 1971–1992 and reported a ratio of 2.67:1, 24 drugs removed in the U.K. versus nine in the U.S. His explanation for the lower number of withdrawals in the U.S. was that the longer period spent examining the data in that country allowed regulators to detect serious safety problems before products were marketed.[20] Estimates suggest that, in the U.S. during the period 1990 to 1995, for every one month's reduction in a drug's review time there was a 1% increase in expected reports of ADR hospitalizations and a 2% increase in expected reports of ADR deaths.[21]

Carpenter and colleagues suggest that the true effect of faster approvals on safety is not the overall rate of withdrawals, but what happens to those drugs approved on the cusp of the approval deadline clock.[22, 23] The Food and Drug Administration (FDA) has a statutory requirement to complete its review of 90% of new drug applications within specific periods of time, depending on whether it is a standard or priority review. If the FDA fails to meet that obligation, then renewal of legislation that allows it to collect user fees from industry may be endangered. The conclusion reached by Carpenter and coworkers was that, when drugs are approved in the immediate pre-deadline period, there is a substantially higher rate of withdrawals and/or safety labelling changes compared to drugs approved after the deadline. In other words, it appears that, if the deadline is imminent, the FDA does a less thorough job of reviewing drugs in order to avoid crossing the deadline and potentially jeopardizing its revenue from drug companies.

Similarly, revenue to the TPD will also suffer if service standards (completion of reviews of new drug applications within the targeted time) are not met. If the actual performance in a given fiscal year is more than 110% of the target for a particular fee category (different types of approval applications are subject to different fees), penalties apply for the amount in excess. Fees are then to be reduced for the next reporting

year by a percentage equivalent to the performance not achieved, up to a maximum of 50%; so if approvals are 20% overtime, fees will drop by 20%.[24] Faced with the prospect of penalties, it is possible that the TPD might follow the pattern set by the FDA and rush to approve new drugs that are approaching the deadline in order to avoid incurring a financial loss in the next year.

Lack of measurable standards for safety

As I have previously noted, Health Canada, through its cost recovery initiative, has committed itself to achieving measurable standards with regard to drug approval times. However, it has no standards for safety issues. As one example, there is no standard for the length of time that it will take between the receipt of an ADR and when that ADR has been analyzed and posted on Health Canada's Medeffect Adverse Reaction Database. The United Kingdom commits to three to seven days to process ADR reports and Australia targets initial professional review of ADR reports within three days. Health Canada has explicitly rejected developing comparable standards, claiming that "development of quantitative service standards for post-market surveillance activities or compliance and enforcement activities is difficult given the unpredictability and volatility of the activities involved."[25]

Absence of information about how decisions are made and no monitoring of the effects of decisions

Although Health Canada has recently issued a draft guidance document about triggers for issuing risk communication documents (available at: http://dsp psd.pwgsc.gc.ca/collection 2007/hc-sc/H164–48–2007E.pdf), it is unclear what methodology and information it uses in making its decisions. As Table 1 shows, out of the nine products that have been withdrawn for safety reasons since August 2004, there were no prior safety warnings for five of them. Were safety issues a complete surprise for these five drugs?; and, if not, then why weren't prior alerts issued? The cases where there were safety warnings raise their own set of questions. The withdrawal of lumiracoxib came less than two months after the safety warning. What happened in such a short period of time to change Health Canada's assessment of the drug? Why were there no additional warnings issued for rofecoxib after April 2002 despite increasing concerns about its safety?[26] The first two safety warnings about gatifloxacin do not appear on the Health Canada web site, and an announcement of its withdrawal is also absent.

When important safety problems are identified with drugs, the company manufacturing the product sends out a notice of the safety issue on behalf of Health Canada to health care providers, and Health Canada posts a notice for the public and health care professionals on its web site. (As noted above, Health Canada can inform the public without the agreement of the manufacturer.) Health Canada does not make any efforts to monitor the impact of the safety information it provides or authorizes. Single letters or web site announcements about safety problems have been shown to have little or no impact on prescribing of drugs.[27, 28] A 2008 article in the Canadian Medical Association Journal showed that, although warnings about the use of atypical antipsychotic drugs in patients with dementia slowed the growth in the use of this type of drug in this group of patients, the warnings did not reduce the overall prescription rate, despite the fact that the warnings discussed serious adverse drug events.[29]

Reporting of ADRs

The backbone of Health Canada's system for monitoring the safety of drugs already on the market is the reporting of ADRs through MedEffect Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php). Health Canada is ahead

of many countries in allowing direct consumer reporting of ADRs and in posting its entire database of ADR reports on a publicly accessible web site.[30] But passive ADR reporting systems world-wide are generally considered to capture only 1-to-10% of all reactions, and that figure may in fact be considerably lower.[31] One French study estimated that, even for serious and unlabelled reactions (reactions not previously included in the official government information about the drug), the estimated reporting rate was one report for every 4,600 reactions.[32]

New Zealand has the highest reporting rate of ADRs of all member countries in the World Health Organization Program for International Drug Monitoring, both in terms of reports per 1,000 doctors and reports per million population.[33] New Zealand's relatively high reporting rate is due to several factors: staff in its Centre for Adverse Reactions Monitoring are committed to providing feedback to individuals filing reports; outreach strategies, such as presentations on a monthly basis to health care providers, are used to promote the Centre's services and activities; education about ADR reporting is integrated into medical curricula; ADRs experienced by individuals are recorded with their National Health Index (NHI) number and therefore knowledge about these reactions is available to hospitals (and increasingly general practitioners), through linkage with the NHI number, so that health-care professionals are sensitized to look for future ADRs in these individuals. At present, Health Canada either does not employ any of these measures or they are minimally used. (Provincial control over health care delivery means that it would require interprovincial agreement in order to have a national system of recording ADRs with health insurance numbers.)

Making safety information available

As was mentioned in the previous section, ADR reports filed with Health Canada are publicly available via a web site. But safety information in clinical trials that are submitted to Health Canada during the approval process is regarded as commercially confidential and will not be released, even under an Access to Information request, unless the company that owns the data agrees. Since 2004, Health Canada has been posting a Summary Basis of Decision for every new active substance (unique molecular entity) that it approves. These documents outline the scientific and benefit/risk-based reasons behind Health Canada's decision to grant market authorization for a product.

The key part of the SBD of importance to prescribers and consumers is the clinical information on drug effectiveness and safety. Is enough information provided to allow for the safe and rational use of new medications? The answer to that question, based on three case studies, is No; there is too little data released to allow outside researchers to independently analyze the safety profile of new drugs.[34]

This lack of access to the safety information in the approval dossier is compounded by the relative lack of published randomized controlled trials (RCTs) that the companies undertake in order to get medicines on the market. Lexchin looked at this question with respect to drugs with novel therapeutic properties introduced into Canada between 1990 and 2000, and found that for many drugs there was a marked lack of published trials at the time of marketing.[35] A more recent article looked at drugs approved by the FDA in the U.S. Over half of the trials submitted to the FDA remained unpublished five years after the drugs were approved, and additionally there was selective reporting of trial results (more positive than negative studies were published) for commonly marketed drugs.[36]

Overall, then, health care professionals and consumers are extremely limited in their ability to get safety information from any source, especially about new drugs.

Safety and progressive licensing

At present, once a new drug is approved for marketing, or in the language of the Food and Drugs Act it receives a Notice of Compliance (NOC), Health Canada is significantly limited in terms of its ability to demand that companies generate new safety information. The aim of progressive licensing is to move from an "all or none situation" — either license the drug or don't — to a position where the safety and efficacy of drugs is followed throughout their entire lifecycle. Here is what Health Canada says about progressive licensing on its web page: "Progressive Licensing means that Health Canada would assess the benefits and risks of a product before and after it reaches the market, establishing a stable regulatory standard that reflects a lifecycle approach to drug regulation."[37]

The promise of this new system is that ongoing re-evaluation of the risks and benefits of medications will pick up serious safety issues earlier and help to better target drug therapy. In April 2008, the Canadian government unveiled new legislation (Bill C-51) incorporating the principles of progressive licensing.[38] Although this legislation died when a federal election was called in the fall of that year, it is worth examining what it proposed, as it is likely that some form of this bill will be re-introduced in the near future.

There were concerns that Bill C-51 would allow some promising new drugs to be fast-tracked to market. The clinical trials that would form the basis for deciding how promising a new drug is are almost always industry-funded and designed to generate data for approval purposes. Often the trials that show promise for serious conditions are stopped before completion on the grounds that it would be unethical to continue to give patients either a placebo or an inferior comparator. Early stopping is becoming more common and these published reports about these trials "often fail to adequately report relevant information about the decision to stop early, and show implausibly large treatment effects, particularly when the number of events is small."[39] To the extent that it relies on trials that are stopped early, Health Canada will need to be extremely vigilant about the safety of any products that it approves under progressive licensing.

Under Bill C-51, Health Canada was to be given the additional authority to issue the market authorization for a drug, subject to additional terms and conditions, and suspend the authorization if the company does not follow through on its obligations.[40] In practice, these new powers likely meant that Health Canada would be able to require companies to carry out post-marketing studies to look at potential safety problems. While in theory this additional information would be valuable in assessing where new products fit into the therapeutic armamentarium, in reality there are worries about relying on industry-funded studies. A narrative systematic review has shown that commercially sponsored research is much more likely to result in positive outcomes than research funded from any other source.[41]

Finally, C-51 entrenched even further the rationale for keeping safety data secret. A clause in the bill specifically cited trade agreements such as the North American Free Trade Agreement (NAFTA) as a reason for not releasing information. The bill also was silent about whether or not the results of industry-funded post-marketing studies would be made public. The use of trade agreements as an argument for refusing to release clinical trial data is hard to countenance, since the FDA routinely posts edited reviewers' comments about new drugs on its web site, and the U.S. is a partner in NAFTA.

Conclusion

Absolute drug safety can never be achieved. The variability in human biology means that all drugs will lead to safety problems in some people. The task for regulatory authorities such as Health Canada is to identify as many as possible of these problems before drugs are released onto the market; then to continue to monitor drugs after approval to ensure that any new safety issues are documented; and finally to be sure that this information is disseminated in an effective manner so that practitioners prescribe and patients use medicines in the safest and most beneficial way possible.

Although the Food and Drugs Act gives Health Canada significant powers, the agency has usually chosen not to use these powers, opting instead for negotiations with the pharmaceutical industry, despite the fact that the values of the industry, based on profit seeking, are nominally not the same as those of Health Canada: protecting the public. Attempts to correct limitations in the Food and Drugs Act in the form of Bill C-51 may actually have made the situation worse.

The way that Health Canada has exercised its legislative authority is mirrored in the priorities that it has adopted. The agency has not fully abandoned the tasks outlined above, but neither has it fully embraced them, as can be seen by looking at how it allocates its resources and how it treats the information that it receives. The organization has accepted the language and, more importantly, the ideology of the private sector and has tailored its activities to ensure that, in the language of its own Business Transformation Strategy, it "reduce[s] the administrative burden on business."[12] We need new and better drugs to improve the treatment that people receive, but not at the expense of downplaying safety, as is now the case.

Within the Canadian drug regulatory system, democratic values such as openness, safety, and objective information are being ignored as Health Canada consciously opts instead for a drug regulatory system that reflect the interests of private industry.

Recommendations

- Health Canada should utilize the powers that it is given through the Food and Drugs Act and act to protect people's

health rather than delay action through negotiations with drug companies.

- Health Canada needs to reorient its priorities so that post-marketing pharmaco-surveillance is on an equal footing with the approval of new drugs.
- Health Canada needs to devote significantly more resources to its post-marketing pharmaco-surveillance system.
- Health Canada should undertake a systematic study to examine whether faster drug approvals lead to more post-marketing safety problems.
- Health Canada needs to develop measurable standards to judge its post-marketing pharmaco-surveillance system.
- Health Canada needs to publicly and transparently explain what criteria it uses in issuing safety communications.
- Health Canada needs to systematically analyze whether its methods of communicating with health care professionals and the public are producing the desired effects.
- Health Canada should study the methods that New Zealand uses in its post-marketing ADR system and adapt them for Canadian use.
- Health Canada needs to stop treating safety information as confidential and commit to making all safety information publicly available promptly after approving a new drug.
- Health Canada should use progressive licensing in order to decrease its dependence on industry for information by ensuring that post-marketing studies are undertaken, analyzed, and reported on independent of industry. Furthermore, progressive licensing should enhance the transparency of safety information rather than further secrecy.

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