# Progressive drug licensing: An opportunity to achieve transparency and accountability?

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∞ See related article page 1845

Health Canada's Progressive Licensing Framework,[1] as described in this issue by Neil Yeates,[2] suggests that the present drug regulation system needs improvement. The most substantive change in the new framework is that Health Canada will take a more active role after a drug reaches the market. In addition, Health Canada's decision-making will become more evidence-based, accountable, efficient and transparent, and there will be an increased focus on patients and drug safety. All are important and highly laudable goals; however, one of the less explicit expectations of the framework is that new drugs will reach the market more quickly. Unfortunately, little information is provided about how drug approvals would be granted more rapidly, and I fervently disagree with any attempt to change the process with faster drug approval as an objective. Although earlier release of new drugs would be welcomed by the pharmaceutical industry, Mr. Yeates also implied that this will not compromise safety, because a new and enhanced postmarket surveillance system will identify problems quickly and effectively. This is speculative and is not supported by evidence or by Health Canada's track record.

At present, the system for reviewing and monitoring prescription drugs in Canada has serious deficiencies and often fails to consider patients as the primary focus. As a consequence, the system frequently does not adequately protect the public from serious adverse drug events. In this commentary, I describe 2 recent examples to support my assertions. I also offer suggestions for potential changes to the present system that, if properly implemented, should help to improve patient safety and to restore the public's trust in Canada's drug approval and monitoring system.

The drug tegaserod (Zelnorm) highlights many of my concerns with the current system. Tegaserod was withdrawn from the market in the United States and Canada in March 2007. In retrospect, tegaserod probably never should have been approved. It was initially marketed in Canada in 2002 for the treatment of irritable bowel syndrome with symptoms of chronic constipation in women. Tegaserod was restricted to women because there were too few men in the clinical trials to demonstrate its efficacy in men. A pooled analysis of placebo-controlled trials provided by Novartis to the US Food and Drug Administration (FDA) led to the withdrawal of tegaserod from the market. This analysis showed that tegaserod increased the incidence of serious cardiovascular adverse events, including myocardial infarction, unstable angina and stroke. The FDA concluded that the drug's overall harm versus benefit profile was unfavourable for continued marketing. As illustrated by this example, withdrawal of a drug from the market is one of the ways that regulators can protect the public from adverse drug events. Unfortunately, drug withdrawals often occur after many patients are severely injured or die. It is also noteworthy that Health Canada rarely initiates drug withdrawals. Withdrawal of a drug from the market and placing of a warning label in the monograph are usually initiated elsewhere (most often in the United States by the FDA). One of the major limitations of the present system is that even if a drug is withdrawn from the market, there is no mechanism for Health Canada to determine whether patients were harmed unnecessarily. I propose the following changes to the new progressive licensing framework to rectify this limitation.

## Make all decisions by Health Canada about drug approval completely transparent

This could be accomplished by listing on an open-access Web site all drug approvals and nonapprovals, as well as a summary of and the rationale behind the decision. In the example of tegaserod, in 2002, the decision to approve the drug could have been posted online with an explanation of how a review of all available evidence showed that the benefits outweighed the harms. If the approval was granted with conditions (e.g., more trials including men needed), the summary document could outline the specific conditions and the timelines that must be met in order to maintain approval. Having this information in the public domain would ensure that pharmaceutical companies are accountable to the public.

In addition, a complete review and all clinical trial data used to reach the decision should be made available to the academic community. Researchers could apply to independently evaluate the evidence and to test novel hypotheses with the available data. Ideally, all new clinical trial or safety data should be posted on this Web site as soon as it becomes available.

Making the current review process transparent would be relatively simple and would have enormous advantages. Decisions and reports would have to be evidence-based and accountable because they would be open to scrutiny. The open-access model would encourage other countries to use Canadian data, to make available their data and to expose any discrepancies. This model would make unpublished clinical trial data available to researchers conducting systematic reviews. Having all the available information in one place would also make it easier to see what additional information is needed.

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**Key points**

- The current system of drug approval and monitoring is in need of a major overhaul
- Some of the proposed changes in the Progressive Licensing Framework, including a patient-centred focus, are laudable
- Health Canada should not focus on speeding up the review process
- Health Canada should provide the rationale for all drug approval decisions to enhance transparency. All clinical data should be made available to researchers in a usable format
- An independent board should be established to review all drug withdrawals and warnings

## Establish an independent board to evaluate prescription drug safety

An independent board is essential to provide oversight of the regulatory process and to keep it accountable. The board should include appropriate experts (e.g., in pharmacology, medicine and clinical trials) who have no conflict of interest and who are independent of the drug industry and the government. The board's first mandate should be to investigate all decisions of drug withdrawal and to answer the following questions: Was the decision to remove the drug appropriate? Should the drug have been approved in the first place? When did the evidence of harm first become known? Did the regulator respond as quickly as possible to protect the public? How many people were unnecessarily harmed by the drug? Could the system be improved based on what was learned from this incident?

In the example of tegaserod, the board would review the information provided by the FDA and judge whether the decision was justified and timely. The board would also review the initial approval by Health Canada and assess whether it was appropriate. After completing its investigation, the board would send the findings and recommendations to Health Canada and make them openly available to the public. Following such a process for even one drug would improve the regulatory system, and over time this self-correcting mechanism would markedly improve drug safety in Canada.

The second mandate of the board should be to investigate and answer the following questions when a drug receives a warning label: What is the purpose of the warning label? Will it protect patients? What evaluation methods have been used to assess whether the warning label protects patients? If the warning label is not protecting patients, should the drug be removed from the market?

This would provide a much-needed mechanism to evaluate whether warning labels have an impact on prescribing. In my opinion, the main purpose of warning labels is to protect the drug company and the regulator from legal recourse and not to protect the public. In fact, warning labels transfer the responsibility for harms caused by a drug to the physician and the patient, often without providing any method for avoiding the harm. In my experience, physicians are often unaware of warning labels, and labels do not change drug prescribing and do not protect patients. I believe that having an independent board would markedly change when and how warning labels are used in Canada.

Consider how an independent board could have helped Canadians address the paradoxical situation of selective cyclooxygenase-2 (COX-2) inhibitors, a subgroup of nonsteroidal anti-inflammatory drugs. Two COX-2 inhibitors, rofecoxib (Vioxx) and valdecoxib (Bextra), have been withdrawn from the market, presumably because the harms outweigh the benefits. In contrast, 2 other COX-2 inhibitors, celecoxib (Celebrex) and lumiracoxib (Prexige), remain available on the Canadian market with a warning label stating that the drugs increase cardiovascular risk. Is this situation rational and evidence-based? The best available evidence from randomized controlled trials shows that all selective COX-2 inhibitors (compared with placebo) are associated with a moderately increased risk of vascular events, largely attributable to a 2-fold increase in the risk of myocardial infarction.[3] How do the warning labels for celecoxib and lumiracoxib protect patients from this increased risk?

There are many potential changes and improvements that are possible in the new regulatory framework. I believe that making drug approval decisions and data accessible on the Internet, as well as establishing an independent board to review all drug withdrawals and warnings are the most important changes. I hope that these suggestions will prompt a debate and, in particular, prompt a response from Health Canada concerning this issue. Improvements to the Canadian drug approval and monitoring system are long overdue.

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