5. Post all of the above information as soon as a drug receives a 'Notice of Compliance' indicating that it has been approved for marketing in Canada.
6. When a drug is approved with a Notice of Compliance with Conditions (NOC/c)[6], publicly post full disclosure of approval conditions on the Health Canada website the same day as the NOC/c is issued.
7. Make material that companies present to fulfill the conditions attached to a NOC/c publicly available.
8. Fully disclose all serious adverse events observed during clinical trials.
9. Make public the clinical trial data on drugs that were denied approval and on drugs that companies voluntarily withdrew from the approval process.
10. Set an upward limit of 25% on the proportion of the budget of Health Canada's Therapeutic Products Directorate (TPD) that comes from industry user fees, with government appropriations making up the balance. This arrangement would reduce the potential conflict of interest associated with industry funding, hence benefiting the transparency initiative.
11. Ensure there is no direct link between drug company user fees and the review process. As with recommendation 10, this would decrease the potential for conflict of interest and benefit the transparency initiative.
12. Ensure that anyone involved in the drug review process who reports wrongdoing will be protected from harm and that the public will be fully informed about wrongdoing in this process. Ensure that everyone has the right to report wrongdoing anonymously and directly to an independent whistleblower watchdog agency.

[1] This policy brief is drawn, in part, from a 25-page position paper of the same title, written by Ann Silversides, that is available at: **www.whp-apsf.ca**.
[2] At the time new drugs are approved there is often little safety information in the peer reviewed literature. Previous research has shown that doctors make little use of the Product Monograph. Therefore, doctors are often forced to rely on the promotional literature when making decisions about prescribing.
[3] These typically appear on the Therapeutic Products Directorate web site 5 to 6 months after the drug was approved.
[4] Figures supplied by Health Canada.
[5] We acknowledge that some off-label use is appropriate and well informed; these are not the instances we are referring to here.
[6] A Notice of Compliance with Conditions from Health Canada means a company can market a drug on the condition that they undertake additional studies to verify its clinical benefit.

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Transparency and the Drug Approval Process at Health Canada[1]

A Policy Brief from Women and Health Protection

The issue

Canada's prescription drug approval process lacks transparency. Much, if not most, of the information provided to Health Canada as part of the drug approval process is treated as confidential. This degree of confidentiality is directly contrary to the public interest. The lack of transparency can lead to inappropriate, unnecessary and sometimes dangerous drug use, and it impedes the development of knowledge and appropriate decision-making.

- Information presented by manufacturers to Health Canada during the drug approval process is not available to health professionals, researchers, provincial drug evaluators and consumer groups. One consequence is that health care professionals may be prescribing drugs without adequate understanding of their risks.[2]

- Women are particularly affected by the lack of transparency because many drugs, such as antidepressants, are prescribed much more frequently for women than for men, and because women tend to live longer than men and the number of drugs taken increases with age. In addition, women typically oversee health care and drug decisions for the family.

- The US Food and Drug Administration (FDA) makes public far more information about its drug approval process than does Health Canada. Canada's lack of transparency stems from a broad interpretation of 'commercial confidentiality,' which extends to unpublished pre-market safety and effectiveness studies. Canada is under no international trade obligation to keep these studies secret.

- Recent revelations have drawn attention to the serious harm associated with some heavily-marketed, widely-used prescription drugs. In most cases, this harm could have been either prevented, or at least recognized much earlier, if Health Canada and other regulators had disclosed, to the public and public interest researchers, more information about the basis on which these drugs were approved.

- There is mounting evidence of bias in the reporting of clinical trials involving humans that pharmaceutical companies submit as the basis for prescription drug approval. Safety problems with drugs may be obscured or buried.

Consumer groups, medical and scientific bodies (including Health Canada's own Scientific Advisory Board), the media, and at least one Parliamentary standing committee have been critical of Health Canada's unwillingness to place the data it receives as part of the drug approval process in the public domain. Health Canada has publicly endorsed the concept of greater transparency, but actions taken so far to achieve this are inadequate.

Current government policy and practice

To have a drug approved for marketing in Canada, the pharmaceutical manufacturer must submit the results of human clinical trials, as well as basic chemistry and laboratory data, animal studies and manufacturing information. Health Canada considers this information to be the property of the drug companies. Researchers and media who seek information about the approval process for a drug must submit Access to Information (ATI) requests. Health Canada then informs the manufacturer of

its intent to disclose and if the company disagrees, it can take Health Canada to court. Even if the company does not take that step, the ATI process is lengthy and time-consuming and the amount of information released under the Act is usually extremely limited.

Health Canada officials have acknowledged the need for more transparency and they have begun to publish Summary Basis of Decisions (SBD) documents[3] for new drugs (for which no similar drug exists). Critics have said, however, that the SBD model does not provide enough information to uncover key safety concerns. In 2005, Health Canada held public consultations on launching an initiative involving the registration and disclosure of clinical trial information (see http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/proj/enreg-clini-info/index_e.html). While policy development plans and timelines have been developed, and an expert advisory committee is planned, this initiative has not yet been implemented.

Meanwhile, the same pharmaceutical companies that insist on secrecy in Canada participate in public hearings in Washington. Far more information about the prescription drug approval process is available in the US, where results of clinical trials (edited to remove manufacturing secrets) are posted on line at the US FDA website. While much of the information is quite technical, American consumer and public interest groups routinely analyse it and produce reports. The FDA's expert advisory committees meet in public, and all background documents for the meetings are made public.

Problems with the status quo

He who pays the piper... In 1994/5, Health Canada introduced a user pay scheme, under which drug companies pay a substantial proportion of the Therapeutic Products Directorate budget (51 per cent in 2004, up from 20 per cent in 1994/5[4]). A danger inherent in this scheme is that the "user" comes to be seen as the group being served—in this case the industry, instead of the public. The interests of the public and the interests of the pharmaceutical industry are not the same, yet this obvious fact sometimes becomes obscured. An open, transparent and rigorous drug approval process, with public scrutiny, would go a long way to counter the perception of bias.

Physicians and their patients may be unaware that they are using medication in a manner for which the evidence of effectiveness and safety is inadequate. Clinical trials of drugs are almost entirely (about 90%) designed and financed by pharmaceutical companies. International experts have documented the ways that clinical trials can be designed and analyzed to produce biased results. Leading peer reviewed medical journals will no longer accept for publication articles about clinical trials, unless those trials were publicly registered, and their endpoints identified, when the trials began. This goes some way to address the problem of "failed" trials that go unreported or unpublished. For example, pharmaceutical companies did not publish trial results that revealed that the use of SSRIs (Selective Serotonin Reuptake Inhibitors, such as Prozac) by those under 19 years of age showed evidence of harm (increased thoughts of suicide), no benefit or extremely modest benefit when compared to a placebo. Because doctors did not have access to this information, they wrote thousands of prescriptions for Canadian teenagers, as well as for younger children.

While registration of trials is an important initiative, it still does not provide public access to the *results* of the clinical trials. Dr. Alan Bernstein, president of the Canadian Institutes of Health Research, noted: "If we are to accelerate the development of cost-effective new interventions, then open and public access to all trials and their outcomes will be key to achieving that goal."

Prescription drug use in the "real world"

Clinical trials typically involve a limited number of people studied for fairly brief periods of time, and very often exclude people who are taking other prescription medications, as well as people who are elderly or have other serious illnesses. After a drug is approved for marketing, it is typically prescribed for far more people, many of whom are older or younger than the carefully selected clinical trial group, and many of whom are also taking other prescription drugs. Adverse drug reactions that did not become apparent in the smaller clinical trial group often appear among the larger group of "real world" patients. The susceptibility of some people to these risks might have been identified in clinical trial results, experts say, but these trial results are not available for public scrutiny. Further, Health Canada does not now systematically track —or require companies to track—the experience of patients who take drugs once they are on the market.

Meanwhile, a growing number of drugs are being prescribed for "off-label" uses—uses that were not approved by Health Canada. Doctors can prescribe off-label "at their discretion". (Prescribing SSRIs to those under 19 years of age is, for example, an off-label use.) In some cases, companies have applied to have already marketed drugs approved for another indication and been refused by Health Canada for safety reasons. This information —a failed application—is not made public. Yet pharmaceutical companies have been known to actively promote off-label prescribing for the uses that have been explicitly refused, or not authorized, by Health Canada. An example is the promotion of Diane 35, a drug approved only for the treatment of severe acne, and only under very specific conditions. Berlex, the manufacturer of Diane 35, funded a report distributed to Canadian doctors affirming that Diane 35 is effective for birth control and that it is safe to use. Healthcare professionals are put in a position of operating with blinders on, and their patients are put unnecessarily at risk, because the information about rejected applications is not publicly available.[5]

> "A central reason for improving transparency is to discipline the regulatory system to a public check on the quality of regulations before they are finalized, and to ensure that the priority is placed on public good regulation, not on private interests."
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> - From "Protection and Precaution: Canadian Priorities for Federal Regulatory Policy - An NGO Position Paper on the Proposed Government Directive on Regulating". Prepared by Hugh Benevides, Canadian Environmental Law Association, Dec. 2005, p.16.

Recommendations for addressing the problem

The Canadian government has acknowledged a lack of transparency in our drug approval process. The government has also expressed a clear intent to remedy the problem and Health Canada has taken some small steps in this direction. We strongly urge that the following additional measures be put in place to achieve the government's transparency objective.

1. Post all clinical trials reviewed by Health Canada to approve a drug, whether published or unpublished, on the Health Canada website.
2. Post all Health Canada reviewer reports, including those that did not support marketing approval for a drug, on the Health Canada website.
3. Conduct expert advisory committee meetings in public, with time set aside for public comment. Make all material that is available to advisory committees publicly available at least one week prior to the meeting.
4. When expert advisory committees have been asked to report on an application for approval, post their full reports.