

# Transparency and the Drug Approval Process at Health Canada

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## Introduction: The growing call for greater transparency

In a fall 2004 speech to health researchers, then Federal Health Minister Ujjal Dosanjh criticized Health Canada's policy of keeping secret the results of clinical trials submitted by drug companies when they apply to have new prescription drugs approved for marketing:

*“Questions have been raised as to whether Canadians are well served when the results of all clinical trials are not publicly disclosed. As an advocate for public health, it is difficult to me to defend such secrecy ... I want to make it clear tonight that I have a bias on this issue in favour of disclosure, and except for legitimate and compelling reasons of privacy or commercial confidentiality, this is the direction in which our Department of Health shall move. I encourage industry and other parties to work with Health Canada toward that goal because there is no turning back....”<sup>1</sup>*

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Well publicized revelations of serious harm associated with heavily marketed and widely used prescription drugs have thrown a spotlight on concerns that vital information about drugs is withheld from the public. This information is being withheld not only by the drug industry, but also by government regulators, presumably mandated to make vital information known.

The recent world-wide recall of the widely-prescribed arthritis medication Vioxx, several years after serious problems with the drug were documented and on file at Health Canada, and revelations about the dangers associated with the use of Selective Serotonin Reuptake Inhibitors (SSRIs), found in unpublished trials known to health regulators, underscore the importance of public access to all clinical data before and after a drug has been authorized for marketing. Moreover, this level of public disclosure is necessary to begin to re-establish the perception that Health Canada is an effective, independent institution that acts in the public, not commercial, interest.

These recent developments also raise questions about Health Canada staff's capability to adequately assess new drug applications. How is it that a drug such as rofecoxib (Vioxx), with proven harm and minimal proven benefit, was approved? External expert groups ask why and how such drugs are approved, but too little information about this process is provided to the medical community, researchers and consumers.

Regulators appear to be comfortable assessing reported drug benefit. But harm — particularly uncommon serious adverse events — remains under-reported. Health Canada repeatedly assures Canadians that its drug approval process is rigorous and of the highest standards.<sup>2</sup> Yet the fact remains: **it is difficult, perhaps impossible, to evaluate the integrity of a process when you can't get basic information about it.** And Health Canada makes public far less information than does its US counterpart, the Food and Drug Administration. Even Health Canada officials refer to the “black box” nature of their own agency's operation.<sup>3</sup>

Drug approval decisions are most important to Canadians in terms of benefit and harm, but costs also enter into the equation. Drugs are the second largest category of health care spending in Canada, after hospitals. Spending on prescription drugs is expected to top \$20 billion in 2006.<sup>4</sup> And the total expenditure on prescription drugs in Canada is rising — an average of 10.8 percent a year between 1985 and 2000 — faster than spending in any other health care category, except capital costs (which represent a much smaller dollar amount).<sup>5</sup> Per person expenditures on prescription drugs in Canada almost doubled from 1998 to 2004.<sup>6</sup>

There is a built-in tension between the federal and provincial roles with respect to prescription drugs: Health Canada approves drugs and the Patent Medicines Review Board oversees pricing, but provinces pick up the tab. As one researcher notes, the federal government “is almost completely insulated from feeling the impact of its policies because, although it regulates drug prices, it does not buy any drugs.”<sup>78</sup>

And provincial drug quality reviewers do something Health Canada doesn’t do: they examine selective data submitted by drug companies in order to ascertain a drug’s effectiveness, and its effectiveness compared to drugs already on the market. (See information on Common Drug Review below.) Provincial evaluators gather this information in order to make recommendations about whether or not the drug should be listed in the provincial formulary. Each province pays all or part of the costs of a drug listed in its formulary and, since new drugs are invariably more expensive, this recommendation has significant cost implications.

Clinical trial results are a key part of the drug approval process. “If we are to accelerate the development of cost-effective new interventions,” Canadian Institutes for Health Research President Dr. Alan Bernstein wrote recently, “then open and public access to all trials and their outcomes will be key to achieving that end.”<sup>9</sup> Currently, trial results are not public.

The definition and treatment of “confidential third party information” appears to be the key factor cited by Health Canada in keeping information from the public. (See Confidentiality and the Access to Information route, below.) However, the International Working Group on Transparency and Accountability in Drug Regulation — a group convened in Uppsala Sweden in 1996 by Health Action International and the Dag Hammarskjöld Foundation — concluded that drug agencies and inspectorates “often maintain secrecy to a much greater extent than law or logic actually demand.”<sup>10</sup> The fact that the US drug approval process is significantly more transparent than Canada’s underscores this point.

### **Transparency — a women’s issue**

The lack of transparency in the drug approval process is important to women, not just for their own health, but because they are typically the health care gatekeepers for the family. They are particularly affected by the culture of secrecy, because they are the family members who most need the information to make appropriate purchasing decisions. For example, if a more transparent system had provided timely information to women about

the risks and lack of efficacy of SSRI antidepressants, how many more women would have balked at filling prescriptions for their children and themselves? SSRIs and other antidepressants are prescribed much more frequently for women than for men.<sup>11</sup>

The important role of parents was acknowledged in the fall of 2004 when a scientific advisory panel of the US Food and Drug Administration (FDA) urged the FDA to insist that parents sign consent forms indicating that they understood the risks before their child began taking SSRIs. As well, the panel suggested that parents be given brochures outlining the pros and cons of SSRI use.<sup>12</sup> No similar policy has emerged from Health Canada or its advisory bodies.

Women use the health care system more than men because of biology, and because they are more likely to engage in preventive and health maintenance behaviours. Indeed, the importance that women place on preventive health maintenance has left them particularly vulnerable to misleading and dangerous claims from drug companies. The extensive promotion of Hormone Therapy (HT) by drug companies as a preventive therapy for menopausal women — to help them maintain youthfulness and prevent heart disease — led millions of women to take HT for lengthy periods and boosted drug company sales. Yet the fact that such use (which was not supported by any clinical trials or observational evidence) actually heightened women's risk of breast cancer and heart disease — the two most common causes of death in post-menopausal women — was not definitively established until 2002, when because of these findings, researchers halted the arm of the Women's Health Initiative trial evaluating the use of estrogen and progesterone.<sup>13</sup>

Similarly, the promotion of routine bone mass density (BMD) testing, which has little predictive value, involves the adoption of definitions that relegate the bone mass of normally aging women to pathological categories. The test is “marketed and promoted in ways that draw on, and perpetuate, two trends in western popular culture: (a) the medical model of the aging female body; and (b) the fear of aging and its association with disability, dependency and immobility.”<sup>14</sup> In the wake of the bone mass density testing comes the promotion of drugs that ostensibly prevent bone fractures but have little or no benefit in preventing that most debilitating of fractures in the elderly — hip fractures.<sup>15</sup>

Safety standards for many prescription drugs are based on clinical trials conducted predominantly on men without separate analysis of effects in women (or the elderly or young of either gender). Because of their different size and physiology, women are more vulnerable to some adverse effects from these drugs. Indeed, many widely-used drugs have posed greater health risks for women than for men.<sup>16</sup> This information — which typically could be ascertained in the drug approval process — is rarely made explicit or public.

As well, women predominate in one demographic group where prescription drug use is highest — the elderly. Yet, for example, women were under-represented in major clinical trials in which people with and without heart disease were randomly assigned to take a statin (cholesterol lowering drug) or a placebo (sugar pill).<sup>17</sup> These drugs have been widely promoted, but in a review of trials involving women, researchers found they could

not conclude that the drugs had any benefit for women with high cholesterol but no cardiovascular disease.<sup>18</sup>

Clearly, women have a particular interest in knowing details about the clinical trials and safety data submitted by companies seeking approval for drugs. And women still need to be better represented in the trials, a position that is endorsed by Canadian participants in the International Conference on Harmonization of Technical Requirements (ICH), a group which is working to blend the approval process for new pharmaceutical drugs in Europe, the United States and Japan. (Canada is not a voting member of the ICH but has committed itself to the ICH principles and contributes to the debates.) See [www.ich.org](http://www.ich.org).

Women are also more likely than men to have natural life experiences framed as medical problems — requiring prescription drugs — and this is especially true in the areas of mental and reproductive health. Indeed, this medicalization of the female experience is worsening. As one manifestation of this process, a recent study of 20 years of US, British and Canadian medical journals found that, while in 1981 there were equal numbers of men and women in advertisements for psychiatric drugs in the Canadian Journal of Psychiatry and its US counterpart, by 2001 the proportion of women had soared to over 80 percent.<sup>19</sup>

### **Drug approval secrecy — some history about the controversy**

The level of secrecy maintained around Health Canada's drug approval process has been criticized by the media, consumer groups, medical and scientific bodies (including Health Canada's own Science Advisory Board), and at least one Parliamentary standing committee. Health Canada, meanwhile, has publicly endorsed the concept of greater transparency in the drug approval process — especially in the past few years. But action on this front has been slow in coming.

In 1995, the director general of what was then called the Drugs Directorate announced Health Canada's intent to produce a document summarizing the basis on which drug approval decisions are made.<sup>20</sup> Only now, ten years later, is this initiative being acted on. The regulatory agency's "intent to move forward with enhanced transparency measures ... has been mentioned at various public forums throughout 2003/4 including Public Policy Forums and the Drug Information Association's First Annual Canadian Meeting, November 2003, in Ottawa, Ontario," according to a government report.<sup>21</sup> However, its soon-to-be launched initiatives have already been criticized as inadequate, with proposals falling far short of the levels of public disclosure which are now the norm in the US. (See Health Canada: Small steps to transparency, below.)

In May 2004, the Canadian Association of Journalists awarded Health Canada its annual Code of Silence Award. In bestowing the award for Health Canada's "efforts to shroud open government", the journalists' association press release took particular aim at the drug approval process, quoting from the report on prescription drugs of the parliamentary all-party Standing Committee on Health, which found "the manner in which drugs are tested and approved is too secretive, in large part due to excessive concerns about the commercial interests of the drug companies."<sup>22</sup>

In early 2004, an open letter, composed by the Canadian Health Coalition and signed by hundreds of Canadians, was sent to Prime Minister Paul Martin expressing alarm about Health Canada's proposal to replace Canada's Food and Drug Act. A key rationale for proposing changes, according to Health Canada, was the Act's "too narrow focus on safety."<sup>23</sup> As one of six key demands, the letter urged the prime minister to "allow full public access to the information upon which federal regulators base approval of a product or technology."

This was not a new demand. In 1998, during Canada-wide public consultations about replacing the Food and Drugs Act, one of the "consistent strong messages was that the lack of public confidence in Health Canada cannot be fully addressed until the activities of the department are made more transparent." Another strong message was that "the right of Canadians to be informed should prevail over the right of industry to have confidential commercial information protected, when disclosure of this information is necessary for the protection of public health."<sup>24</sup>

A report from Health Canada's own Scientific Advisory Board found that the current drug review process is "unnecessarily opaque." Canada can "at least emulate the standards of our nearest and largest trading partner," concluded the report, which was released in early 2000: "No observer can fail to be struck by the fact that the same companies that insist on secrecy when it comes to their applications in Canada are perfectly prepared to send senior scientific and management representatives to public hearings in Washington, there to present details of their research and answer detailed questions on the science supporting their applications to the FDA."<sup>25</sup> (See Other jurisdictions, below.) The report dismisses arguments that domestic law and international treaties require that Health Canada maintain a high level of confidentiality: "Canada would not be subject to any action under these treaties if we adopted procedures which were no more transparent than those of our largest trading partner, the United States." The Science Advisory Board report argued that "safety and well being of the person must take precedence over considerations of commercial advantage or bureaucratic process."

Four years later, a report on prescription drugs by the Parliamentary Standing Committee on Health observed that individual Canadians "may be harmed by the lack of scrutiny and by a dearth of independently assessed information . . . The committee does not support a clinical trial system that discourages openness in order to protect commercial interests."<sup>26</sup> The committee recommended that Health Canada introduce measures to ensure public confidence, starting with a public database that provides information on clinical trials in progress, trials abandoned and trials completed.

### **The prescription drug approval system**

Health Canada's drug approval process falls under the responsibility of the Health Products and Food Branch (HPFB), formerly known as the Health Protection Branch.<sup>27</sup> A number of directorates and offices fall under the aegis of the HPFB. The prescription drug approval process is handled by the HPFB's Therapeutic Products Directorate (formerly known as the Therapeutic Products Programme). Biologics — blood products,

vaccines and drugs derived from biotechnology — are approved by another directorate, the Biologics and Genetic Therapies Directorate.

To have a drug approved for sale in Canada, the pharmaceutical manufacturer has to test it on cells and tissues, on animals and, finally, on people, in order to ensure that the drug is acceptably safe and effective. The manufacturer must submit to the regulator basic chemistry, laboratory data, animal studies, and manufacturing information, as well as the results of clinical trials. The company must submit the results of all clinical trials to the regulator, regardless of their outcome.<sup>28</sup>

The information provided to Health Canada by drug companies is considered, by Health Canada, to be proprietary to the drug companies. Researchers and media who seek information about the approval process for any given drug must submit Access to Information (ATI) requests. Health Canada then informs the company of its intent to disclose information and, if the company disagrees with the regulatory body's plans, it can take Health Canada to court. (See Confidentiality and the Access to Information route, below.) But even if the company does not take Health Canada to court, the amount of information released under ATI can be extremely limited, and the process is lengthy and time-consuming. Members of the public do **not** have access – or have very limited access – to the following information:

- the names of the drugs in the regulatory approval system;
- results of clinical trials;
- full comments of Health Canada reviewers about information submitted;
- information about indications applied for, but refused authorization, in the case of drugs that are approved for another use;
- names of drugs that are refused authorization to market (i.e., drugs that receive a Notice of Non Compliance);
- the conditions placed on drugs that receive a Notice of Compliance with Conditions (NOC/c) (\*this may be changing, see NOC/c below);
- the full reports of Expert Advisory Committees, including rules concerning selection of members.

The procedure in the US is markedly different. The FDA routinely makes considerably more information about the drug approval process public, whether or not the drug companies agree to the release of the information. (See Other jurisdictions, below.)

## **What we don't know**

### **Names of drugs in the regulatory approval process**

In Canada it is not possible, pre-approval, to find out the names of drugs that have been submitted to Health Canada for approval — at least not from Health Canada. The drug company itself, on the other hand, is free to make this information available. In the US, the name of a drug in the approval process is made public by the FDA on those occasions when an expert advisory committee is convened to consider the submission. Other New Drug Applications (NDAs) are not made public by the FDA, but drug manufacturers

often make them known to investors. As well, information about NDAs can be found in US Securities and Exchange Commission documents and, often, in the US financial press.

### **Results of clinical trials**

In order to gain approval for a new drug, pharmaceutical companies must submit to the regulator the results of clinical trials. In Canada, this information is considered proprietary to the drug company. Independent and public interest researchers and the public are unable to scrutinize the basis on which a drug receives approval in Canada. Even provincial drug evaluators, whose job is to recommend whether a drug should be listed in a provincial formulary so that eligible patients have drug costs at least partially covered, don't have access to all the clinical trial information. But drug regulatory agencies are servants of the public, entrusted with the responsibility of protecting and advancing health with respect to drugs. By keeping this information secret, Health Canada is placing proprietary and commercial interests above those of the public.

In medical, scientific and consumer circles, concern is growing about the secrecy of Canada's drug approval process. Recent documentation about the way some clinical trials are conducted and reported has set alarm bells ringing. At issue is how clinical trials, most of which are effectively controlled by the pharmaceutical company manufacturer, can be (and are) manipulated to produce biased results, and how the results of "failed" trials (that show harm, or no benefit, from a drug) can go unreported or unpublished.<sup>29</sup> Leading peer reviewed medical journals now stipulate that, as of June 2005, they will not accept articles about clinical trials of drugs unless those trials are publicly registered when the trials begin.<sup>30</sup> Registration creates a trail, making it more difficult to suppress unfavourable results. And since drug companies don't know in advance which trials will have favourable results (the ones they are more likely to seek publication for), this condition should prompt more routine registration of trials.<sup>31</sup>

The Canadian Institutes for Health Research recently announced that all randomized controlled trials that it funds must be registered so that information can be posted on a public web site. But CIHR president Alan Bernstein noted: "Trial registration is an important initiative, but it is not a panacea. *It will not provide access to trials submitted to regulatory agencies, a major source of trials. 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*"<sup>32</sup> (emphasis added).

Health Canada has been monitoring, collaborating on, and/or participating in a number of ongoing and existing domestic and international initiatives relating to clinical trial transparency. These include the International Committee of Medical Journal Editors requiring registration of clinical trials as a prerequisite for publication, and the World Health Organization (WHO) International Clinical Trial Registry Platform Working Group, of which Health Canada is a member, which will launch an international Clinical Trials portal in May 2006. As well, many individual companies have created their own publicly accessible registries and results databases. **However, registration alone will not give the public access to the full results of clinical trials submitted to approve drugs.**

The International Working Group on Transparency and Accountability in Drug Regulation, in a 1996 statement, observed that, among other consequences, secrecy impedes development of knowledge (particularly dangerous where suspicion arises of a hitherto unknown risk), can serve to hide malpractice, and may facilitate use of substandard drugs and irrational drug use.

Issues that surfaced regarding the clinical trials for SSRIs illustrate the points made by the International Working Group. In June 2004, Health Canada issued a warning about the class of antidepressants known as SSRIs because of their potential for harm, including the risk of self-harm. This risk of harm applied to everyone taking the drugs, but was of particular concern because of the number of young people taking the drugs. Unknown to the doctors prescribing drugs to this age group, clinical trials that had been conducted in under-19-year-olds showed evidence of harm, no benefit, or extremely modest benefit from the drugs when compared to a placebo.<sup>33</sup>

These trials were submitted to Health Canada as part of the drug approval process but, as is the current policy of the regulatory agency, were not available to anyone outside the agency. Pharmaceutical manufacturers, meanwhile, had simply chosen not to publish those trial results that did not cast a positive light on their product (only six of the 15 trials conducted on children and adolescents have been published).<sup>34</sup> SSRIs are being prescribed to thousands of Canadian teenagers. According to IMS Canada, a private health information company, treatment with medication was recommended to 80 percent of those 18 and under seeking help for depression in 2002.<sup>35</sup> Health Canada's June 2004 advisory notes that SSRIs are not authorized for use in patients under 18 years of age and states that doctors prescribe them for this "off label" use "at their discretion." The advisory does not provide any more details about the efficacy (or lack thereof) of these drugs.<sup>36</sup>

But in prescribing these drugs to teenagers, doctors had access to "an incomplete and inaccurate representation of the totality of evidence.... When we are guided by meta-analyses carried out of biased datasets, we are operating under the illusion of practising evidence-based medicine," concludes a Therapeutics Letter on antidepressant medications in children and adolescents from the University of British Columbia Therapeutics Initiative.<sup>37</sup>

An article in the Canadian Medical Association Journal put the case more bluntly: "The secrecy that surrounds the drug approvals process means that physicians and their patients may be unaware that they are using a medication in a manner for which the evidence of effectiveness and safety is inadequate. Such policies value commercial interest above that of patients."<sup>38</sup>

If Health Canada did not make the SSRI clinical trials on teenagers and children public, how were the results of the unpublished trials scrutinized? They were posted on the US FDA website following the enactment, in 2002, of the Best Pharmaceutical for Children Law.<sup>39</sup> That law provides incentives, in the form of extra patent protection, to drug

companies that do clinical trials on children, a practise that Health Canada is currently considering.

### **Full comments of Health Canada reviewers**

The reports of Health Canada reviewers are not made available, except sometimes through Access to Information (see Getting Information below), although they reveal much about the drug approval process and may include the reasoning of those in favour, and those not in favour, of approving a particular drug. Health Canada reviewer reports were denied even to provincial drug evaluators until recently when, at least for those evaluators involved with the Common Drug Review (CDR) initiative, they became available.<sup>40</sup> The CDR is a federal initiative, launched in late 2003, to review drugs and recommend to provincial governments whether or not they should be added to provincial formularies. (Provincial governments have, however, retained their own drug review procedures.)

In a move towards improving transparency in decision-making, a Summary Basis of Decision initiative was undertaken in 2004-05 by Health Canada. A Summary Basis of Decision is a document that “outlines the scientific and benefit/risk based considerations that factor into Health Canada's decision to grant market authorization for a drug or medical device.”<sup>41</sup> The document includes regulatory, safety, efficacy and quality (chemistry and manufacturing) considerations. More information about the Summary Basis of Decision initiative can be found at: [www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/proj/sbd-smd/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/proj/sbd-smd/index_e.html).

Critics of the process at a consultation workshop held in Ottawa in June 2004 argued for stronger input from consumers in the decision-making process, more transparency (specifically posting on HC's website) in the steps towards approval or lack of approval, and improved post-market surveillance once drugs are approved.

### **Indications applied for, but refused authorization**

Information about indications that were applied for, but not approved by Health Canada, is also vital since so many drugs are prescribed “off label” — i.e., for uses that have never been authorized. (Sometimes, the companies never sought approval for these uses, but sometimes approval was refused because companies did not submit data that was convincing enough.) Physicians can prescribe drugs off label “at their discretion”, as Health Canada notes. This is legal even though the regulator has not ruled on a drug's safety or efficacy for the off label use, and even though there may be no evidence about safety or efficacy. Federal legislation applies only in that it prohibits promotion for unapproved uses.

Although comparable Canadian figures are not available, a US newspaper investigation found that 21 percent of the prescriptions written for top selling drugs are prescribed for off label uses. The investigation looked at the three top selling drugs in 15 classes of medications. It also revealed that off label prescribing nearly doubled in the five years from 1998 to 2002.<sup>42</sup> The off label prescribing of drugs is, increasingly, actively sought

by pharmaceutical firms since it is an effective way of enlarging the market for a drug without having to undertake expensive clinical trials.

If a drug company applied for and was denied approval for a particular use, the public needs to know why, especially if that unapproved use is being widely sought by the drug company and the drug is being prescribed for that unapproved use. As the International Working Group on Transparency and Accountability in Drug Regulation noted, if a drug is subject to negative findings, and the drug regulatory agency does not make this public, that omission “can leave the way clear for the sometimes very different and emphatic account given from the manufacturer.”<sup>43</sup>

An example that affects Canadian women is Diane-35. This drug was approved by Health Canada only as a treatment for “severe acne unresponsive to oral antibiotics, with associated symptoms of androgenization, including seborrhea and mild hirsutism.” Diane-35 was not approved for use as an oral contraceptive, nor was it approved as a first-line treatment for acne. (The drug had been used as an oral contraceptive in Europe, but its use was restricted because of liver toxicity.<sup>44</sup>) It is not known whether or not the manufacturer, Berlex, actually applied to Health Canada for approval of Diane-35 as an oral contraceptive. However, Health Canada reviewers did express serious concerns about the safety of Diane-35, which we know because of Health Canada reviewer reports that the Canadian Broadcasting Corporation (CBC) program, “Disclosure”, obtained through Access to Information.

In one document, Berlex reportedly questioned Health Canada’s request for more study of safety data “given the fact that the product will neither be indicated nor promoted for oral contraception.”<sup>45</sup> However, subsequent to its approval in 1998, and despite its restricted approval and the safety concerns associated with it, the drug has been actively presented to doctors as an oral contraceptive<sup>46</sup> and promoted directly to young women — in print advertisements in university women’s washrooms and magazines, as well as on television and in movie theatres — to treat regular acne. Sales jumped 45 percent between 2000 and 2001<sup>47</sup> and Health Canada took no action and issued no warning until contacted by the CBC program Disclosure for comment.<sup>48</sup>

A recent British Columbia court case centred on the off label use of the epilepsy drug Topamax, which was prescribed for pain. Plaintiff Dana McCartney argued he had suffered brain injuries in a car accident four years earlier, while the Insurance Bureau of British Columbia (IBBC) had argued that it was, instead, the off label use of Topamax that led to McCartney’s depression and difficulty thinking. The IBBC is appealing the decision, which went in the plaintiff’s favour.<sup>49</sup>

South of the border, the arthritis drug Bextra was promoted, through articles published in a dental journal, for the treatment of acute pain; sales subsequently increased significantly. But the Washington-based watchdog organization Public Citizen sued the US FDA for unpublished information about the approval process and discovered that Bextra was explicitly rejected for use in treating acute pain because of safety concerns.<sup>50</sup>

The lesson: in the absence of transparency about the drug approval process, drug companies can (and do) promote drugs for uses that may have been explicitly rejected.

### **Notice of Compliance with Conditions**

A Notice of Compliance with Conditions (NOC/c) from Health Canada means a company can market a drug on the condition that they undertake additional studies to verify its clinical benefit. To receive a NOC/c a drug “must be of high quality and possess an acceptable benefit/risk profile ... [although] the clinical benefit of these drugs has not yet been verified,” according to a fact sheet on NOC/c from the Therapeutic Products Directorate (TPD), posted on the HPFB website. When the conditions are met, the conditional tag will be removed, the website states. The NOC/c category was created in May 1998 and first used in July of that year for the AIDS antiretroviral drug Rescriptor.

At the time of writing, Health Canada has not made public the nature of the conditions placed on a drug that receives an NOC/c, but have indicated their intention to do so by the end of 2005.<sup>51</sup> Until then, prescribing doctors and patients are left in the dark about what risks might be involved in taking the drugs. Under a February 2003 policy revision, Health Canada states an intention to publish the NOC/c Qualifying Notice (QN) “which provides in general terms (i.e., non-proprietary) the commitments required of sponsors in order to proceed with authorization under the NOC/c policy.... the NOC/c-QNs are to be posted to the Health Canada website in an effort to enhance transparency of the process.”<sup>52</sup> It remains unclear, at the time of writing, within what time frame such information will be available.

The rationale for NOC/c is to fast track drugs for life threatening conditions such as AIDS and cancer. It was, therefore, a surprise when Relenza, a new drug for “uncomplicated” influenza, received an NOC/c designation in 1999. In the US, a Federal Advisory Committee had recommended against approving the drug, since the largest trial in North America showed it reduced the length of time someone suffered from influenza by half a day. (The FDA overruled its advisory committee and approved the drug anyway.)<sup>53</sup> Meanwhile researchers with the University of British Columbia’s Therapeutics Initiative, an independent organization set up to provide doctors and pharmacists with timely, evidence-based, practical information on drug therapy, were unable to find out exactly what conditions were placed on the drug’s notice of compliance.<sup>54</sup> In material prepared for patients, Glaxo Wellcome (Relenza’s manufacturer) did not mention the conditional nature of the marketing approval. “The subject of conditional approval is complex and is very unlikely to be meaningful to a patient in the absence of an appropriate explanation from a health care professional,” the chief medical officer of Glaxo Wellcome in Mississauga, Ontario explained.<sup>55</sup> When a complaint was brought to the Pharmaceutical Advertising Advisory Board (PAAB) because brochures did not state that conditions were placed on Relenza’s notice of compliance, the PAAB agreed with the complainant and “referred the case to Health Canada for an opinion on the necessity of including the fact, that a product was issued a NOC/c, in patient information brochures.”<sup>56</sup> On Sept. 18, 2003, Health Canada published a revised policy on NOC/c and accepted the PAAB recommendation.

### **Expert advisory committees**

Health Canada sometimes convenes expert advisory committees to provide advice about the approval of particular drugs. The regulator now posts on the Internet brief summaries of the deliberations of these committees, which meet in private; but the summaries provide only a glimpse into what was discussed. And the criteria for these committees — for example, the appointment process — are not available to the public. This is in stark contrast to the situation in the US where the deliberations of similar advisory committees are public, as are all the background documents supplied to them.<sup>57</sup>

For example, the report of a March 2000 meeting of Health Canada's TPD expert advisory committee on HIV therapies, posted on the Internet, notes that members were asked to reveal conflict of interest information with respect to the drug to be discussed (abacavir sulfate). "Where a conflict of interest had been disclosed, it was reviewed by the internal Standing Committee and recommendations were made to manage it. Actions were taken at the meeting to manage all disclosed conflicts of interest in a preventive manner," the report noted. It would seem that what the conflicts were, and how they were "managed" is not a matter for public consumption. In the US, serious concerns have been expressed about the impact of the conflicts of interest of members of similar advisory committees.<sup>58</sup>

More recently, in the creation of an expert advisory panel on silicone gel breast implants (September 2005), Health Canada took steps to post panel members' declared statements of conflict of interest on a public website. Some members did declare conflicts of a financial nature in the form of monies for past work or consultation received from the manufacturers of the products under review. While Health Canada's decision to make these declarations public was laudable, their good intentions were weakened by their subsequent decision to dismiss the relevance of these conflicts.<sup>59</sup> Clearly there is still some distance to go in making the expert advisory committees and panels more transparent and accountable to the public.

### **Getting information**

#### **Confidentiality and the Access to Information route**

The definition and treatment of "confidential third party information" is at the heart of the issue when it comes to Health Canada's track record of keeping information from the public. This is not the only problem, but it is central. There are valid reasons to protect manufacturing secrets and the identities of patients in clinical trials. However, Health Canada "protects" far more information than this. Important information from clinical trials and expert reviewers about the safety and effectiveness of drugs is virtually impossible to obtain.

In Canada, at the present time, you must file a request under the Access to Information Act (ATI) if you want to obtain information about the approval process for any given drug. Filing ATI requests can be a "difficult, long, formal process," acknowledges Serge Durand, the manager of the proprietary and scientific information assessment section of the TPD.<sup>60</sup> Documents that are released are often heavily edited. Section 20 (1) of the

ATI states that the head of a government institution “shall refuse to disclose any record requested” that contains a) trade secrets, b) “financial commercial scientific or technical information that is confidential information supplied to a government institution by a third party and is treated consistently in a confidential manner by the third party, c) information the disclosure of which could reasonably be expected to result in material financial loss or gain to, or could reasonably be expected to prejudice the competitive position of a third party, or d) information the disclosure of which could reasonably be expected to interfere with contractual or other negotiations of a third party.”

The Information Commissioner of Canada, in a special report to Parliament, called for the abolition of 20 (1) (b) and questioned whether 20 (1) (a) was necessary if 20 (1) (c) was in place. The Commissioner comments: “With government downsizing and privatization, more and more matters affecting the public interest are dealt with by the private sector. Government officials and private firms *should not be able to agree among themselves to keep information secret. Yet paragraph 20 (1) (b) comes perilously close to giving authority to just such a cozy arrangement*”<sup>61</sup> (emphasis added). The Science Advisory Board report found that the Therapeutic Products Programme (TPP), now the TPD, procedures are at odds with a 1998 judgement with respect to the ATI which found that the onus rested with a company to show why information should not be disclosed. The TPP procedures “seem to enjoin secrecy unless there is a requirement that information be disclosed... Significant improvement in transparency can be achieved simply by interpreting the Act as it is meant to be interpreted: with a presumption of disclosure unless an exemption is clearly warranted.” In any event, the Act can be amended to clarify the limited application of the Act to the drug review process, the report concluded.

The access to information route has not been effective or satisfying, judging from the experience of four public interest applicants. In the late 1990s, Dr. Joel Lexchin sought to discover why Canada had approved treatments for a paediatric anti-diarrhoeal drug when the World Health Organization had decided the drug had no place in managing acute diarrhoea in children. He filed an ATI request. He waited more than 21 months for a reply and eventually received a document with almost everything blacked out.<sup>62</sup> More recently (summer 2004), Lexchin filed several ATI requests and was informed that the waiting period for receipt of the information would be at least four months, rather than the legislated 30 days, because of Health Canada’s shortage of resources.

Also in the late 1990s, doctoral student Barbara Mintzes filed an ATI request to find out more about a contraceptive product. She waited one year for information. Applying to the FDA under the US Freedom of Information Act, she received the information within two weeks. In a more recent related incident, it took CBC reporters, using access to information requests, more than five years to get access to Health Canada’s Adverse Drug Reaction database in a searchable form<sup>63</sup> — a database containing information of direct relevance to the public. When it finally received the information and analysed it, the CBC found that, since 1997, there was a threefold increase in adverse reactions, including deaths, among children. Health Canada had not noted this alarming trend, because it had not analysed the information that it had. (See Results of Clinical Trials

above for discussion about prescribing of SSRIs to children. Many drugs prescribed for children have not been tested on children and hence are prescribed off label.)

Before releasing any information under ATI, Health Canada officials must inform the sponsor (the drug company) of intent to disclose the information (section 27/28 of the Act). If a sponsor disagrees with the officials about the extent of disclosure, it can take Health Canada to court. There are now 14 court cases outstanding as a result of such appeals.<sup>64</sup> “Our goal is to disclose information we consider not confidential: Most of the time, the company says this is confidential.... we need more complaints about this,” Durand said. Meanwhile, the director of ATI for Health Canada observed that legislation “may not have intended” the company’s use of the appeal process to block disclosure.

Applicants can also appeal when they are refused information, as public interest researcher Ken Rubin did after the government refused to release the full text of a report titled “Special Review on the Safety of Calcium Channel Blockers.” Controversy surrounds the safety of this type of drug and Rubin appealed Health Canada’s decision to release only a highly edited version of the review, arguing there was a public interest in having the safety concerns revealed. Section 20 (6) of the Act states that, notwithstanding the confidentiality provisions, the head of a government institution may disclose information if disclosure would be “in the public interest as it relates to public health, public safety” and if such disclosure “clearly outweighs” any prejudice to a sponsor’s competitive situation. His appeal failed. The Federal Court trial decision rested on the point that while a government official may disclose in the public interest, he/she does not have “the obligation to do so.”<sup>65</sup>

Researchers with the CBC, meanwhile, were more successful in their ATI requests about the process of approving the drug Diane-35. Although the process took at least a few months, the CBC was able to obtain copies of reviewers’ reports on the new drug submissions from Berlex Canada. The drug had, however, been on the market for several years before the ATI request was launched.

Clearly, using access to information does not appear to be a satisfactory route to gaining information about the drug approval process in a timely fashion. Answering requests takes up an enormous amount of government employees’ time and, as it happens, about 90 percent of the requests about drug product files (which account for more than half the ATI requests filed with the entire Health Canada department) come from pharmaceutical companies or their agents. And while the government is obliged to keep this “third party information” confidential, the sponsor company is free to make public whatever it wants. Hence Health Canada has found itself in the unusual situation of refusing to release information that is already posted on a company’s website.<sup>66</sup>

## **Other jurisdictions**

### **The United States**

Much more information about the drug approval process is publicly available in the US than in Canada. As previously noted (see p. 7), drug company management

representatives present details of their research and answer questions in public fora when they are seeking FDA approvals. Yet they insist on keeping the same information secret when they are seeking approvals in Canada.

Indeed, Canadians who seek information about a drug approved in both countries can log on to the US FDA website and find their way to a wide range of information — including the clinical trials that companies submitted with their application for licensing approval and reviewer notes, both of which are unavailable in Canada. Much of the information on the FDA website may be rather too technical for non-professionals, but consumer and public interest groups in the US routinely analyse such information and produce reports.

In the US, information is also available about some not-yet-approved drugs. For about one-third of new drug submissions, the FDA decides it needs outside help in evaluation and convenes a federal advisory committee. Everything the committee examines and discusses is public, although documents are often posted only in the 24 hours prior to the committee meeting. While expert advisory committees are sometimes convened to help with the drug approval process in Canada, only a brief summary of their deliberations is made public.

The US FDA also has a history of being more willing than Health Canada to release information about the drug approval process after a drug has been approved. Up until 1997, applicants had to file Freedom of Information (FOI) requests to get that information, but were rewarded with more information than is currently available under Canada's Access to Information process.<sup>67</sup> A 1997 amendment to the US FOI Act allowed federal agencies to post the most requested information without waiting for FOI requests. Now clinical trial and other information for new chemical entities is posted on the FDA website within 10 weeks. Before posting the information, FDA officials edit it to remove any manufacturing secrets and information that would identify patients. They are not required to defer to or consult with the drug company sponsor before posting the information.

### **European Medicines Evaluation Agency (EMA)**

In Europe, the EMA (the equivalent of Canada's Therapeutic Products Directorate, TPD) issues European Public Assessment Reports (EPARs) that are "supposed to reflect the assessment file submitted by the manufacturers, its analysis by the EMA's scientific advisory body and the reasons underlying that body's opinion."<sup>68</sup> The EPARs were analysed by the International Society of Drug Bulletins, an organization founded in 1986 with the support of the World Health Organization, comprised of independent bulletins that publish articles on drugs and therapeutics. The Society found the documents were uneven and not reliable — they do not always have epidemiological data or describe the mechanism of action of the drug and they were not updated regularly.<sup>69</sup>

Meanwhile, new community legislation regarding access to EMA documents appears to have important parallels to Canada's ATI Act, and to mirror the latter's shortcomings. For example, although there is a "presumption of access", the legislation builds in a requirement to consult with companies before disclosing information.<sup>70</sup> And full clinical

trial results submitted to the regulator “will remain confidential” EMEA spokesmen told a Health Canada consultation.<sup>71</sup> The EMEA does plan, however, by November 2005, to provide information about the reasons why drugs are not approved and information explaining the withdrawal of drugs from the market. “Now as regulators we can’t explain [withdrawals and negative decisions],” a spokesman said, who then mused about “why we as regulators are confined, when companies can inform on things any time.”<sup>72</sup>

### **Health Canada: Small steps to transparency**

As part of a 5-year initiative called the “Therapeutics Access Strategy” (TAS) launched in 2003, Health Canada is piloting the publication of Summary Basis of Decisions (SBDs). These publications summarize the basis for approving a new drug. (The name implies that the decision to refuse to approve a new drug, or a particular application of a drug, will also be summarized, but this is not the case.) In the first phase, SBDs will be created for drugs that are new active substances — drugs that have a different molecular structure from those already on the market.

The intended audience for the SBD is “the informed consumer”, including provinces and private payers who want information and those writing treatment guidelines, explained Dr. Robert Peterson, the former Director General of the TPD.<sup>73</sup>

The US FDA published Summary Basis of Approval documents until 1994, when this approach was abandoned — “a shift was made to disclose redacted [edited] reviews to alleviate the burden on review staff involved in the preparation of SBAs.”<sup>74</sup> (While they provide far more information, these redacted reviews are not always user-friendly — they can be difficult to read.)

A year after the US discontinued their summaries, Dann Michols, the Director General of the Drugs Directorate (now the Therapeutic Products Directorate) began talking about a Canadian SBD, though three years later he hedged, arguing that creation of SBDs “is difficult to justify as the Programme strives to meet existing performance targets for all submission types.” Health Canada finally, in 2004, opted to produce SBDs and hired technical writers to produce them. Still, the TPD acknowledges that information now made public in the US “contains far greater detail than the proposed Canadian SBD.”<sup>75</sup>

Health Canada is currently undertaking a Registration and Disclosure of Clinical Trial Information initiative. It intends to hold consultations on options and impacts in early 2006, and a recommendation to the Minister is forecast for Spring 2006. Stakeholder consultations were held in June 2005 with a view towards improving “end-user” access to clinical trial information. More information on the Registration and Disclosure of Clinical Trial initiative can be found at:

[www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/proj/enreg-clini-info/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/proj/enreg-clini-info/index_e.html).

The initial model SBD documents produced by Health Canada were for the cholesterol-lowering drug Crestor, and Fabrazyme, an enzyme replacement for use in Fabry’s disease. Interestingly, less than two weeks after Health Canada held a “multi-stakeholder consultation” (in June 2004) to consider the two model SBDs, it issued a warning about

Crestor, because use of the drug had been linked to kidney failure and kidney damage. Meanwhile a newspaper article about Fabrazyme revealed that the price tag is \$290,000 a year for each patient.

An analysis by Dr. Joel Lexchin and Dr. Barbara Mintzes of the information in the model SBDs concluded that the lack of detailed information meant the documents would not be useful in uncovering safety concerns, since they will not provide enough information to reveal bias in trials or ascertain the risk benefit ratio of the medication.<sup>76</sup> In fact, a number of consumer groups told the multi-stakeholder consultation that SBD documents would be useful only if they were a user friendly portal to the simultaneous provision of far more information, such as the details of clinical trials submitted to support new drug submissions and reviewers' notes.<sup>77</sup>

At the 2004 consultation, pharmaceutical industry representatives and then TPD Director General Dr. Robert Peterson repeatedly noted that the SBDs must “respect” the Access to Information Act. This suggests that industry will insist on being able to continue to define what is “confidential” and that government will continue to defer to industry. Industry’s other concerns about the SBD initiative, as stated at the consultation, are that it not take up the time of Health Canada reviewers to the extent that the length of the approval process is affected, and that making public any clinical trial information might jeopardize the publication of such information in a scientific journal. (Although theoretically a possibility, the latter has not been the experience in the US, according to Larry Sasich, a pharmacist with Public Citizen.)

As for Health Canada, Dr. Peterson told the consultation that a major stumbling block to greater transparency is a lack of money and the additional costs associated with ensuring that any information published by Health Canada be in both official languages. But critics say there is no requirement for scientific information (such as clinical trial data) to be translated, companies often already have a French version of submissions and, if there are costs, they can be picked up by the drug companies.

While there is greater disclosure of information in the US, it is not acceptable for Canadians to have to rely on obtaining information about the drug approval process from the FDA website. For one thing, companies may seek approval in Canada before they seek approval in the US and they may seek approval for drugs that have been rejected by the FDA, in which case no information would have been released south of the border. But companies also use different sets of data to seek approval here, and they may seek approval for different indications. As well, the opinions of Canadian reviewers may differ from those of their American colleagues.

### **The complications of industry funding**

Drug regulators in Health Canada have arguably stronger ties to the pharmaceutical industry as a result of significant changes made to drug regulatory operations in the past decade. Meanwhile, public access to information about the regulatory process remains strictly limited. A key change has been the way in which the drug regulatory function is funded. In 1992, the Prescription Drug User Fee Act enabled the US FDA to collect fees

from drug companies in order to speed up reviews of new drug applications.<sup>78</sup> Two years later, Health Canada followed suit, although in Canada drug-company fees replaced government money, while in the US the money was supplemental to government appropriations.

Cost recovery was launched in Canada in 1994/5, when just over 20 percent of the Therapeutic Products Programme (the forerunner of the TPD) budget came from industry fees, with the balance from government appropriations. By 1998/9 cost recovery accounted for just under 75 percent of the total budget.<sup>79</sup> The latest figures (April 2004) show 51 percent of revenue from cost recovery with the balance from government appropriations.<sup>80</sup>

A danger inherent in a “user pay” scheme is a tendency to see the “user” as the client and for this attitude to become pervasive. Indeed, by 1997, the Director General of the TPP was advising staff in an internal bulletin that, “the client is the direct recipient of your services. In many cases this is the person or company who pays for the service.” The public, in this bulletin, is not the government’s client, but rather its “beneficiary” or a “stakeholder”.<sup>81</sup> When companies come to be seen as the customers, the regulators “want to be able to help them, because they realize the enormous research and the resources that have gone into the clinical trials. So they want to be able to deliver a positive message for them.”<sup>82</sup>

In Canada, as in the US, the advent of “user pay” has helped to speed the drug approval process, though not as quickly or to the extent that pharmaceutical companies wish. This speed up has been framed as an initiative to address public concern. In the fall 2002 Speech from the Throne, the federal government committed \$190-million in new money over five years “to ensure Canadians have faster access to the safe drugs they need.” But it is the pharmaceutical industry that has been pushing hardest for faster approval times.<sup>83</sup>

Meanwhile, the push to speed the drug approval process can have other consequences. For example, in the US, a 2003 review by the Office of the Inspector General reported that 40 percent of FDA drug reviewers who had been with the agency five years or more reported the review process has worsened — it was not as rigorous in terms of in-depth, science-based reviews.<sup>84</sup> No similar survey has been done in Canada.

Instead of directly funding the operations of drug regulators, drug company payments could be added to general government revenues (with regulators being apportioned a budget from there), hence breaking the direct link between companies and regulators. But if any kind of “user pay” system of drug approval is to remain in place, the best way to counter a bias, or perception of bias, is an open, transparent and rigorous drug approval process with external scrutiny.

## **Conclusion**

Drug regulatory agencies are servants of the public, entrusted with the responsibility of maximizing the safety and efficacy of drugs. They must be accountable to the public, and the public and the scientific community must be able to ensure, through access to relevant

information, that the agencies are acting in the public interest. The fact that Health Canada's drug approval process is shrouded in secrecy is directly contrary to the public interest.

By keeping information about the drug approval process secret, the federal government is protecting drug companies instead of protecting the public. It is treating information about drug safety as a commodity with a monetary value to companies, rather than a public resource. Most strikingly, Health Canada maintains a much higher level of secrecy than does the US, which is the home of some of the largest and most powerful pharmaceutical companies.

Health Canada insists that Canada has "one of the most rigorous drug approval systems in the world." It will not, however, "open the books" to allow independent and public interest researchers to examine that assertion by studying the operation of the drug approval system. Meanwhile, given recent revelations of the many ways that drug companies have skewed clinical trial protocols and the presentation of clinical trial results in order to promote their products, it is abundantly clear that the more these trials are scrutinized, the better.

While Health Canada takes small steps (such as preparing Summary Basis of Decision documents) towards what it says will be greater transparency, observers are growing impatient. Indeed, the former federal Minister of Health and the President of the Canadian Institutes of Health Research are two recent high profile critics who have joined the ranks of those calling for greater transparency in Health Canada's drug approval process.

For women, the question of safety is paramount. Women are typically the guardians of not just their own, but their extended family's, health. Secrecy can allow unsafe practices to exist. In the words of the International Working Group on Transparency and Accountability in Drug Regulation, secrecy "can serve to hide malpractice, and facilitate use of substandard drugs and irrational drug use." This is not in anyone's interest. Accordingly, Women and Health Protection makes the following recommendations.

### **Recommendations**

1. Post all clinical trials reviewed by Health Canada to approve a drug, published and unpublished, on the Health Canada website.
2. Post all Health Canada reviewer reports, including those that did not support approval, 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.

5. Post all of the above information after a drug is approved, but before it is available for sale in Canada.
6. When a drug is approved with a Notice of Compliance with Conditions, publicly post full disclosure of conditions placed on the approval 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 during clinical trials.
9. Make public clinical trial data from drugs denied approval and from drugs that companies voluntarily withdraw from the approval process.
10. Set an upward limit of 25% on the proportion of the budget of the Therapeutics Products Directorate that comes from 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.

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<sup>1</sup> Hon. Ujjal Dosanjh, address to the Leaders' Forum for Health Research in Canada, Ottawa, Sept. 29, 2004. Health Canada web reference [www.hc-sc.gc.ca/ahc-asc/minist/health-sante/speeches-discours/2004\\_10\\_01\\_e.html](http://www.hc-sc.gc.ca/ahc-asc/minist/health-sante/speeches-discours/2004_10_01_e.html). Accessed February 6, 2006.

<sup>2</sup> "Canada has one of the most rigorous drug approval systems in the world and one of the best safety records," boasts a May 2004 Health Canada information bulletin about cross-border drug sales. Health Canada web reference [www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2004/2004\\_pharmbk3\\_e.html](http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2004/2004_pharmbk3_e.html). Accessed February 6, 2006.

<sup>3</sup> Abby Hoffman, head of Health Canada's Therapeutics Access Strategy, made this comment in her address to the June 10, 2004 Health Canada public consultation.

<sup>4</sup> Morgan, Steve, et al. The Canadian Rx Atlas, Centre for Health Services and Policy Research, University of British Columbia, December 2005.

<sup>5</sup> Information from Canadian Institute for Health Information's report *Drug Expenditure in Canada, 1985 to 2003*, and an interview with CIHI statisticians.

<sup>6</sup> Morgan, Steve, et al, op cit.

<sup>7</sup> Anis, A. Pharmaceutical Polices in Canada: another example of federal-provincial discord. *CMAJ*, Feb. 22, 2000.

<sup>8</sup> One exception is drugs prescribed to registered Indians. While these are not directly purchased by the Federal government, they are federally paid for.

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- <sup>15</sup> See discussion of osteoporosis and analysis of clinical trial results in Abramson, John. *Overdo\$ed America, The Broken Promise of American Medicine*. New York: HarperCollins, 2004.
- <sup>16</sup> In the United States, “eight of the 10 drugs removed from the market between 1997 and 2000 posed greater health risks to women than to men, according to a report by the General Accounting Office, Congress’ non partisan audit agency.” Quote from Simon V, Resnick E. *Drug Therapy and Gender*. *U.S. Pharmacist*, 29(09), 2004.
- <sup>17</sup> See article, “Do Cholesterol-Lowering Drugs Benefit Women,” posted by the Center for Medical Consumers ([www.medicalconsumers.org](http://www.medicalconsumers.org)), which states that women made up less than one-third of study participants in randomized controlled clinical trials of statins.
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- <sup>24</sup> Health Canada Legislative Renewal Issue Paper, Confidential Commercial Information, June 18, 2003.
- <sup>25</sup> Science Advisory Board to Health Canada, report of the committee on the drug review process, February 2000.
- <sup>26</sup> House of Commons, Canada. Opening the Medicine Cabinet: First Report on Health Aspects of Prescription Drugs. Report of the Standing Committee on Health, Bonnie Brown M.P. Chair, April 2004.
- <sup>27</sup> This name change, in particular the removal of the word “protection”, is seen by some observers as symptomatic of a perceived wider shift in Health Canada away from protecting the public interest and public safety towards promoting the interests of industry. See McBane, above.
- <sup>28</sup> Information from Siddika Mithani, Director (at the time), Bureau of Cardiology, Allergy & Neurological Sciences, Therapeutics Products Directorate, Health Canada, in written correspondence with Joel Lexchin.
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- <sup>33</sup> Antidepressant Medications in Children and Adolescents. *Therapeutics Letter*, issue 52, April/May/June 2004, Therapeutics Initiative, University of British Columbia.
- <sup>34</sup> Ibid.
- <sup>35</sup> See Bongers A, Drugs Gone Bad. *The Hamilton Spectator*, Sept 22, 2004. The article states: “IMS Canada, a private health information company, reports rates of use peaking in 2002, when 81 per cent of those 18 and under seeking help for depression were recommended treatment with medication. Last year the rate dropped to 70 per cent.”
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- <sup>41</sup> Personal correspondence between WHP Coordinator Anne Rochon Ford and Heather Throop, Therapeutics Access Strategy Secretariat, December 6, 2005.
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- <sup>44</sup> Mintzes B. Drug Regulatory Failure in Canada, the case of Diane 35. Women and Health Protection, October 2004. Web reference: [www.whp-apsf.ca/en/documents/diane35.html](http://www.whp-apsf.ca/en/documents/diane35.html).
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- <sup>46</sup> See Practice Highlights, *Diane-35, is it an oral contraceptive?* This document was supported by an “unrestricted education grant from Berlex Canada.” A disclaimer says that the views in it are not necessarily those of the Society of Obstetricians and Gynaecologists of Canada or of Rogers Media (distributors of the report).
- <sup>47</sup> Wooltorton E. Diane-35 (pyroterone acetate): safety concerns. *CMAJ*, May 27, 2003.
- <sup>48</sup> Interview with CBC researcher Andreas Wesley, July 2004.
- <sup>49</sup> “B.C. case looks at ‘off label’ use of epilepsy drug”, CBC news March 4, 2003. Web reference: [www.cbc.ca/stories/2003/03/03/Consumers/Topamax\\_030303](http://www.cbc.ca/stories/2003/03/03/Consumers/Topamax_030303). Accessed February 6, 2006.
- <sup>50</sup> Interview with Larry Sasich of Public Citizen, Fall 2004. See also [www.citizen.org](http://www.citizen.org).
- <sup>51</sup> Personal correspondence between WHP Coordinator Anne Rochon Ford and Heather Throop, Therapeutics Access Strategy Secretariat, December 6, 2005.
- <sup>52</sup> Quote from e-mail from Jirina Vlk, Health Canada media officer, Oct. 27. 2004. See also policy document, posted on the Internet at [www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/noc\\_drugs\\_conditions\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/noc_drugs_conditions_e.html). Accessed February 6, 2006.
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- <sup>55</sup> Michael D. Levy, letter to the editor, *CMAJ*, June 13, 2000.
- <sup>56</sup> Pharmaceutical Advertising Advisory Board report. April 2000.
- <sup>57</sup> Although drug company and FDA material are posted before the meeting of an FDA advisory committee, they are often not posted until the day before the hearing (correspondence from Leonore Tiefer, New York, Oct. 20, 2004). When an expert advisory committee is convened to consider a safety issue, related to an already-approved drug, material is posted as much as a week in advance (interview with Larry Sasich of Public Citizen, Nov. 2004).
- <sup>58</sup> Cauchon D. Number of drug experts available is limited. Many waivers granted for those who have conflicts of interest. *USA Today*, Sept 25, 2000. Page A1.

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- <sup>59</sup> In response to a query from Women and Health Protection about these conflicts, the Office of Consumer and Public Involvement of Health Canada defended their inaction by stating that, “the panel has an advisory function only – Health Canada makes the decision” and “a panel member is only one voice among many on the panel.” For full set of correspondence see: [www.whp-apsf.ca/en/documents/concerns.html](http://www.whp-apsf.ca/en/documents/concerns.html).
- <sup>60</sup> Interview with Serge Durand, July 2004.
- <sup>61</sup> Office of the Information Commissioner of Canada. Response to the Report of the Access to Information Review Task Force, Sept 2002, Appendix A, Part B – Legislative Tune up.
- <sup>62</sup> Lexchin J. Secrecy and the Health Protection Branch. *CMAJ*, Sept 8, 1998.
- <sup>63</sup> The CBC efforts to make this database publicly available are described in their story “Faint Warning”, available at [www.cbc.ca/news/adr/](http://www.cbc.ca/news/adr/). Accessed February 6, 2006.]
- <sup>64</sup> Interview with Sue Lajoie, director of Health Canada’s Access to Information and Privacy Division, July 2004.
- <sup>65</sup> Office of the Information Commissioner of Canada, Annual Report 2001-2002, Chapter IV, The Access to Information Act in the Courts.
- <sup>66</sup> Interview with Serge Durand.
- <sup>67</sup> Through FOI, applicants could obtain essentially the same information which is now automatically posted on the FDA website, which is considerably more than can be obtained in Canada through ATI. (Interview with Larry Sasich of Public Citizen, Nov. 2004).
- <sup>68</sup> Prescrire International, June 2002, quoted in Transparency in Drug Regulation: Mirage or Oasis.
- <sup>69</sup> The analysis was of 9 EPARs published by the EMEA between Sept 1996 and August 1997.
- <sup>70</sup> Presentation by Noel Wathion and Martin Harvey Allchurch to Health Canada Summary Basis of Decision External Consultation, June 10, 2004.
- <sup>71</sup> Ibid.
- <sup>72</sup> Ibid.
- <sup>73</sup> Robert Peterson, concluding remarks to Summary Basis of Decision External Consultation, June 11, 2004.
- <sup>74</sup> Health Canada, Issues Analysis Summary, Summary Basis of Decision, Draft 7, Health Canada.
- <sup>75</sup> Ibid.
- <sup>76</sup> Lexchin J, Mintzes B. “An assessment of the usefulness of Health Canada’s Summary Basis of Decision documents in uncovering serious problems with medications”, 2004.
- <sup>77</sup> See “Conditions for endorsement of the transparency initiatives” as presented at the end of the June 10-11 consultation. Accessed at [www.pharmawatch.net/viewnews.php?item=20](http://www.pharmawatch.net/viewnews.php?item=20), August 2004. [this link is now broken. But the reference form is correct. The Pharmawatch website seems to be gone or inaccessible]
- <sup>78</sup> Office of the Inspector General, Department of Health and Human Services. FDA’s Review Process for New Drug Applications: A Management Review. March 2003. Web reference: [www.oig.hhs.gov/oei/reports/oei-01-01-00590.pdf](http://www.oig.hhs.gov/oei/reports/oei-01-01-00590.pdf). Accessed February 6, 2006.
- <sup>79</sup> The Drug Review Process in Canada, a presentation to the Science Advisory Board by Dann Michols, Oct. 1998.
- <sup>80</sup> Figures supplied by Health Canada.
- <sup>81</sup> Cited in “Transparency in Drug Regulation, Mirage or Oasis”.
- <sup>82</sup> Mary Wiktorowicz, Associate Professor at York University’s School of Health Policy and Management, quoted in Eggerston L. Drug approval system questioned in US and Canada. *CMAJ*, Feb. 1, 2005.
- <sup>83</sup> Lexchin J. New directions in drug approval. *CMAJ*, 171(3), August 3, 2004.
- <sup>84</sup> Office of the Inspector General, 2003.