Transparency in Drug Regulation: Mirage or Oasis?

By Joel Lexchin MD

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Executive Summary

DRUG REGULATION IN CANADA is carried out in a very secretive manner because of the unique relationship between the Therapeutic Products Directorate, the arm of Health Canada in charge of approving new drugs, and the brand-name pharmaceutical industry. Because of a lack of resources the TPD it is forced to cede some of its authority to the industry. In addition, both the TPD and the pharmaceutical companies regard information about safety and efficacy as a commodity to be guarded rather than as a resource to be shared. This interpretation is reinforced by the Access to Information Act. As a result it is extremely difficult to get any information about safety and efficacy of new drugs from the TPD.

Recently, there has been increasing concern about the lack of transparency due to industry funding of the operations of the TPD. Reliance on the industry for operating revenue has lead to a tilt in the TPD in favour of industry. Evidence from the United States shows that industry funding may result in lower approval standards. Without access to the data that TPD reviewers are analyzing, the suspicion continues that industry funding has weakened review standards.

Another reason to be concerned about the lack of transparency is that when new drugs appear on the market the volume of published literature that is available to guide prescribing and use of these drugs is often extremely limited. The unpublished material that companies submit to the TPD could potentially overcome this problem but this data is unavailable.

Although there are valid reasons to protect manufacturing secrets and the identities of patients who have taken part in clinical trials these arguments do not apply when it comes to health and safety data. There is no good evidence to show that the interests of companies would be harmed by the disclosure of this type of information; specifically, confidentiality is not necessary to foster research and innovation.

Since 1995 there have been a number of attempts to increase transparency in the drug approval process, most notably a report from Health Canada's Science Advisory Board but all of these efforts have come to naught. In addition, the European Public Assessment Reports which summarize information about new drugs and which Health Canada is looking to as a model for improved transparency have been unsuccessful because of a lack of standardization of these reports and an unwillingness to disclose sufficient clinical information.

There are currently three proposals at various stages of discussion and implementation in Canada for increasing transparency. The one that is the

most advanced is the publication of a Summary Basis of Decision for that would outline the scientific and benefit/risk-based reasons for the decision to approve a new drug. In order to assess the adequacy of the information in these SABs four case studies are presented where access to information given to regulators has lead to the discovery of significant problems with medications. In none of these four cases would the amount of information in the SABs have been enough to uncover the problems.

In the United States after a drug has been approved the Food and Drug Administration routinely posts an approval package that contains a detailed summary of the information that the company has submitted along with the FDA reviewer's analysis of this information. There is no justification for Canada not matching the U.S. standard.

Besides better access to information about drugs that have been approved other measures are needed to increase transparency in the approval system. Canada should also emulate the FDA's system of public expert advisory committee hearings for new drugs, albeit with stronger conflict-of-interest rules than the FDA has. Safety and efficacy data also needs to be available for new drugs and new indications for old drugs in cases where the approvals were refused or where the company withdrew the application.

Box 1 – Access to Information Act

Third Party Information

20. (1) Subject to this section, the head of a government institution shall refuse to disclose any record requested under this Act that contains (*a*) trade secrets of a third party; (*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.

20. (6) The head of a government institution may disclose any record requested under this Act, or any part thereof, that contains information described in paragraph (1) (*b*), (*c*) or (*d*) if that disclosure would be in the public interest as it relates to public health, public safety or protection of the environment and, if the public interest in disclosure clearly outweighs in importance any financial loss or gain to, prejudice to the competitive position of or interference with contractual or other negotiations of a third party.

I. Introduction

THE PHARMACEUTICAL INDUSTRY and the Canadian government have long had a close relationship based on a form of interaction known as clientele pluralism. This situation occurs where the state has a high degree of concentration of power in one agency (the Therapeutic Products Directorate (TPD) a branch of Health Canada), but a low degree of autonomy.

With respect to pharmaceuticals, in Canada, government regulation of drug safety, quality and efficacy is almost solely the responsibility of the TPD. But the state does not possess the wherewithal to undertake the elaborate clinical and pre-clinical trials required to meet the objective of providing safe and effective medications. Nor is the state willing or able to mobilize the resources that would be necessary to undertake these tasks. Therefore, a tacit political decision is made to relinquish some authority to the drug manufacturers, especially with respect to information that forms the basis on which regulatory decisions are made.

On-the-other-hand, the association representing nearly all of the multinational companies operating in Canada, Canada's Researched-Based Pharmaceutical Companies (Rx&D), is highly mobilized to assume a role in the making and implementing of drug policy. It operates an elaborate committee structure, has the ability to act on behalf of its members and the capacity to bind member firms to agreements. (There is an association of generic pharmaceutical manufacturers, the Canadian Generic Pharmaceutical Association, but its members are responsible for less than 15% of drug sales in Canada.) In clientele pluralism, the state relinquishes some of its authority to private-sector actors, who, in turn, pursue objectives with which officials are in broad agreement.

One way this relationship is manifested is the agreement between the industry and the TPD that all of the information that companies submit as part of the regulatory approval process is deemed confidential and will not be released without the express consent of the company involved. Health Canada's own Science Advisory Board agrees that "in general, the Health Protection Branch [now the Health Products and Food Branch] has . . . taken a very cautious position on what it releases as public information." This willingness to keep information secret is reinforced in the Access to Information Act that states that "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." (See Box 1) The Act does provide a way to allow the release of information "if that disclosure would be in the public interest as it relates to public health, public safety " but that provision has never been used in this context. In the late 1990s, an Ottawa researcher challenged Health Canada in the Federal Court of Canada seeking the release of information about a class of drugs known as calcium channel blockers

but the exemption was upheld (Ken Rubin, personal communication).

As a result obtaining even the barest form of clinical information from the TPD about drugs is exceedingly difficult. In the mid 1990s, I became interested in the question of why Canada had licensed products for the treatment of acute pediatric diarrhea when the World Health Organization had concluded that these medications should not be used. Accordingly, in November 1996 I made a request through the Access to Information Act for "all studies that the Health Protection Branch has that deal with the question of the efficacy of: Donnagel, Donnagel-MB, Donnagel—PB, Imodium, Kaopectate or Lomotil in a pediatric population with acute infectious diarrhea." I did receive some information as a result of this application but after a wait of 21 months the final package contained 5 pages from the dossier on Imodium: the title page, the table of contents, the title of a table and two pages with column headings with all of the data removed.

This approach to releasing the clinical information that companies submit reflects a common understanding between officials in Health Canada and the pharmaceutical industry of medical information as a commodity with commercial value that must be protected. Such information can be "loaned" to the government for purposes of review but the companies do so with the expectation that the review will produce material gains through marketing of their products. This market based view stands in marked contrast to a view that data on health and safety is something that should be shared directly with the people most affected – those who prescribe and use the products. What we have instead is information filtered through, and protected by, the officials in Health Canada.

II. Causes for Concern

i. Industry funding of the TPD

In recent years with the introduction of cost recovery there has been a growing concern that the already tight relationship between the government and the industry has been further strengthened leading to a pro-industry bias in drug approvals.

When the federal government was in the full throws of deficit fighting back in the early 1990s, it significantly cut the budget for the TPD (and many other government agencies) and as a result, the TPD turned to cost recovery to obtain the funds necessary to keep running. As a result by 1999, industry was contributing about half the $70 million used by the TPD. In return for these payments, the industry is asking for action on the speed with which new drugs are approved and in the 2003 federal budget $190 million was committed to improvements in the TPD, primarily to decrease approval times. Other evidence of the increasing tilt towards industry comes from the lenient attitude towards direct-to-consumer advertising that should be illegal under the Food and Drugs Act

In the mid 1990s, a working group from the Therapeutic Products Programme (TPP, predecessor to the TPD) looked at ways of efficiently managing its limited resources and came up with a series of recommendations for moving submissions through the system more rapidly. However, the working group admitted that "the pharmaceutical industry is looking for dramatic improvement in service" and "the implementation of the proposed changes may not result in the level of improved performance desired by our industry clients." This pressure prompted the task force to recommend that Canada consider relying more on foreign drug reviews in its approval process. The recommendation was subsequently approved by senior management in the TPP.

Perhaps the most revealing statement about this reorientation of the relationship between the government and the industry came from Dann Michols, the Director General of the TPP. In an internal bulletin distributed to TPP staff in February 1997 he discussed the question of who is the TPP's client. In the context of cost recovery Mr. Michols advised staff 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 one page document focused on service to industry relegating the public to the secondary status of "stakeholder" or "beneficiary".

Evidence that cost sharing and shorter approval times might compromise safety and efficacy standards when it comes to approving new drugs comes from south of the border. There user fees paid to the Food and Drug Administration (FDA) by the brand-name pharmaceutical industry were tied to quicker approvals by the FDA, with times dropping for new molecular entities from 27 months in 1993, when user fees were instituted, to 19 months in 2001. The Washington based Public Citizen Health Research Group surveyed FDA reviewers in 1998 for their reaction to the changes in the agency. Nineteen out of 53 medical officers identified a total of 27 new drugs in the past three years that they thought should not have been approved but were; 17 said that standards were

"lower" or "much lower" than they had been three years previously. A subsequent survey by the Office of Inspector General confirmed some of these findings. Although 64% of FDA respondents had confidence in the FDA's decisions regarding the safety of a drug, at the same time 40% who had been at FDA at least 5 years indicated that the review process had worsened during their tenure in terms of allowing for in-depth, science-based reviews.

Without access to the data that TPD reviewers are analyzing the suspicion continues that industry funding has weakened review standards.

ii. Inadequate knowledge of drugs at time of marketing

When new drugs come onto the Canadian market the amount of published material is often grossly inadequate to allow physicians to make rational prescribing decisions and consumers to make informed choices about whether or not to use these medications. For some drugs there are only single published randomized controlled trials (RCTs, the gold standard in evidence). In other cases, drugs that are intended for long-term use have only been studied for six months or less. Often there are only comparisons against placebos not against other drugs used for the same condition. Even in RCTs, safety data is frequently inadequately reported. Ioannidis and Lau have examined the completeness of safety reporting in RCTs in seven medical areas. Severity of clinical adverse effects and laboratory-determined toxicity was adequately defined in only 39% and 29% of trial reports, respectively. Only 46% reported on the reasons for discontinuations due to toxicity.

Trial data that rests with the TPD may help correct some of these deficiencies but at this time, this information remains locked up in the TPD archives and will only be released with the agreement of the company that submitted it.

III. Is There a Rationale For Secrecy?

THERE ARE CLEARLY GOOD REASONS why manufacturing information should be protected by the TPD. This is proprietary knowledge and if it became public it could adversely affect the financial status of a company by providing competitors with an unfair advantage. Personal data that enters the files of regulatory agencies like the TPD can include the identity of individual patients or health professionals as well as information on the illness from which the patient is suffering. Information that might lead to the identification of individual patients or health professionals should also not be disclosed to any party (International Working Group on Transparency and Accountability in Drug Regulation 1996).

These arguments do not apply when it comes to health and safety data. There is no good evidence to show that the interests of companies would be harmed by the disclosure of this type of information; specifically, confidentiality is not necessary to foster research and innovation. On-the-other-hand, nondisclosure has serious disadvantages for the TPD, health professionals and the public. If information submitted to regulatory agencies is never disclosed then this data will never enter the normal peer review channels and is therefore not subject to scrutiny by independent scientists. Without this type of feedback TPD reviewers may be more prone to misjudge the accuracy or usefulness of the data submitted; the scientific atmosphere in the agency may be stifled and the professional growth of its staff severely inhibited. Deprived of any independent access to information, health professionals have to accept the TPD's judgment about the safety and effectiveness of products. In the case of well-established drugs this is probably not much of a concern, but it may be different with new drugs where experience is limited.

Finally, the public may be denied knowledge of the full health effects of products so that they can decide for themselves whether or not to use them. Even if most consumers would never take the time to read health and safety data, consumer oriented media in consultation with scientific experts could use some of this information to inform the public of the risks and benefits of products.

IV. Previous Proposals to Increase Transparency in the Drug Approval Process

SINCE 1995, there have been a number of abortive efforts to increase transparency in the drug approval. (See Box 2) Especially noteworthy was the report of Health Canada's own Science Advisory Board (SAB). The SAB was set up in 1997 by Allan Rock, then Minister of Health, to advise the Minister on all matters of science as they affected medications, food and medical devices. The SAB formed an ad hoc Committee on the Drug Review Process because of a perceived lack of confidence in the regulatory process. Although the SAB admitted that the review was not comprehensive, the Committee circulated questionnaires to stakeholders and TPD employees, met with senior officials in the TPD as well as officials in the FDA, the Medicines Control Agency in the United Kingdom and the European Agency for the Evaluation of Medicines.

The Committee's 2000 report firmly stated that "in our view and that of many stakeholders, the current drug review process is unnecessarily opaque. Health Canada persists in maintaining a level of confidentiality that is inconsistent with public expectation and contributes to a public cynicism about the integrity of the process." In order to remedy this situation the Committee recommended "that HPB [Health Protection Branch, now Health Products and Food Branch] should set new standards of access to information at all stages of the drug review process, enhancing transparency and public confidence. We perceived no justification for current levels of delicacy regarding 'commercial confidentiality'. We would note: (a) Canada can at least emulate the standards of

Box 2 – Previous Transparency Initiatives

December 1995
- Dann Michols (Director General, Drugs Directorate): "A Canadian Summary Basis of Approval is also being considered as we streamline and standardize the review practices. . . In addition, a project on the role of the Drugs Directorate in information dissemination to consumers and health practitioners is underway."
- Nothing further heard for 2 years about either initiative.

April 1998
- Stakeholder Letter from TPD requesting input into proposal to make public names of drugs in approval process.
- Nothing further heard about this proposal.

June 1998
- Dann Michols once again referred to development of Canadian Summary Basis of Approval: "additional time [to prepare such a document] is difficult to justify as the Programme strives to meet existing performance targets for all submission types." He then went on to talk about a strategy for information dissemination that was initiated in 1997.
- Nothing further heard about either Summary Basis of Approval or strategy for information dissemination.

February 2000
- Health Canada, Science Advisory Board, "Report of the Committee on the Drug Review Process" Recommendation 8.5: Enhance transparency in the drug review process.
- Nothing further done.

openness of our nearest and largest trading partner: [the FDA's procedures will be discussed below] (b) New legislation should provide for public hearings where appropriate; (c) If a product has gone through the FDA's public hearing process, this information should become part of the TPP's NDA [New Drug Application] review process, and the applicant should be responsible for providing copies of transcripts and videotapes". Like previous efforts this one too amounted to naught.

V. A Failed Model From Europe

A RECENT HEALTH CANADA DOCUMENT on increasing transparency [see Section VI(iii) below] favourably refers to the European Public Assessment Report (EPAR) which is a document produced by European Medicines Evaluation Agency (EMEA) after a drug has been approved. EPARs are supposed to reflect the assessment file submitted by the manufacturer, its analysis by the EMEA's scientific advisory body and the reasons underlying that body's opinion. The International Society of Drug Bulletins (ISDB) an international organization of independent drug bulletins with 52 members undertook an analysis of 9 EPARs issued between September 1996 and August 1997. The most striking finding was a lack of standard presentation of information, for instance, the Scientific Discussion section did not consistently include an introduction, it did not always have epidemiological data and in some EPARs the mechanism of action of the drug was not fully presented. The reporting of clinical trials was not always clear and none of the 9 EPARs mentioned references to published trials. Expert opinions along with the doubts and final positions of the experts were of variable quality. The ISDB subsequently extended its analysis to cover all EPARs published in 1999 and 2000. The results were still very negative: the EPARs were not harmonized, reliable or correctly updated.

La revue Prescrire, a French drug bulletin considers that the EPARs have continued to deteriorate in quality. They have "no documentary resources independent of drug companies. In many cases, analysis of EPARs suggests that these documents are totally or mainly written by the firms themselves, or edited by copying and pasting from the firms's application. . . Irregular publication of their updates on the EMEA website means that their value is highly uneven".

VI. Current Proposals for Reform

i. Health Protection Legislative Renewal

Proposals to reform the system have recently appeared from a number of quarters. As part of its efforts to reorganize Canada's health protection legislation, Health Canada put out a discussion document in the summer of 2003. A number of measures are suggested to provide for more openness but at the same time Health Canada seems to have accepted certain limitations in how far it is willing to go and to have foreclosed other options. For instance, the document points out that sections of the North American Free Trade Agreement and the Trade-Related Aspects of Intellectual Property Rights Agreement "provide that the government must protect the confidentiality of undisclosed test or other data provided by the applicant to determine whether the use of such products is safe and effective, where the origination of such data involves considerable effort" although "this does not apply however in cases where the disclosure is necessary to protect the public or where steps are taken to ensure that the data is protected against unfair commercial use." Health Canada proposed that only a summary of the safety and effectiveness data submitted by the manufacturer would be made generally public. If consumers or health professionals want to see the full set of data the proposal calls for a "reading room where people could review all the data submitted by the manufacturer but not transcribe or copy it, or otherwise make that data available to interested members of the public".

ii. Standing Committee on Health

In June 2003, the House of Commons Standing Committee on Health initiated hearings into a wide range of issues affecting prescription drugs and over two months in the fall of that year had a series of open meetings across the country where it heard briefs from a variety of individuals and organizations. When it issued its report the following spring it called for increased transparency and more accountability by Health Canada. To this end, it supported the development of mechanisms to enable public disclosure of information about clinical trials without jeopardizing either the intellectual property rights of drug companies or the privacy of individuals involved in the clinical trialsand it recommended a "public database that provides information on trials in progress, trials abandoned and trials completed".

iii. TPD and the Summary Basis of Decision

In late winter 2004 Health Canada announced that it would publish a document entitled "Summary Basis of Decision" related to drug submissions and medical device applications. The SBD would outline the scientific and benefit/risk-based reasons for Health Canada's decision to grant market authorization for a product. The announcement was followed up with a more detailed document whose opening statement laid out the case for greater transparency: "Transparency is a fundamental good regulatory practice and a clear expectation of the

Canadian public". The "Scientific Discussion" section of the EPAR was explicitly cited as the model for the proposed SBD.

Out of the three proposals that have been put forward, the use of SBDs is the most advanced and therefore merits a detailed analysis. The key part of the SBD document from the point of view of prescribers and consumers is the clinical information that it contains. Is there enough information to allow for safe and rational use of new medications. The best way to analyze the quality and quantity of information in the SBDs is to take examples of where access to unpublished data submitted to drug regulators has uncovered important clinical information about either the safety or effectiveness of drugs on the market and then see whether the same discoveries would have been possible using the SBDs. Health Canada has published two pilot SBDs that can be used in this regard, one for rosuvastatin (Crestor) , a cholesterol lowering medication, and agalsidase beta (Fabrazyme) , an enzyme replacement for use in Fabry's Disease.

a. Celecoxib

Celecoxib is a COX-2 inhibitor marketed for analgesia and inflammation. Its purported benefit over older anti-inflammatory agents (NSAIDs), such as ibuprofen and naproxen, is that it causes fewer serious gastrointestinal side effects. A study published in JAMA (Journal of the American Medical Association) in 2000 appeared to confirm this assertion and showed significantly less gastrointestinal toxicity with celecoxib compared to traditional NSAIDs after six months of treatment. However, material on the web site of the FDA revealed a number of discrepancies between the data as published in JAMA and as submitted to the FDA. The published trial actually combined the results of two trials one that continued for 12 months and the second that ran for 16 months. According to the FDA's statistical reviewer the most appropriate period of analysis should have been the entire study period not the 6 months as reported. Furthermore, according to the study protocol the overall findings of the trial had to be statistically significant before exploratory analyses on subgroups would be conducted. This part of the protocol was not followed and the authors made conclusions about subgroups despite the lack of significance in the primary study outcome. Finally, and most importantly, at the 12-16 month time there was no difference in gastrointestinal adverse effects between the celecoxib and traditional NSAID groups.

Thus the published article presented a misleading impression both of trial design and conclusions. The trial was not 6 months in length; it was 12 to 16 months in length. It did not find evidence of superior safety for celecoxib; the two comparators (ibuprofen and naproxen) were found to be just as safe, including gastrointestinal safety. Given the lack of evidence of superior effectiveness for celecoxib, this difference is far from academic.

Information necessary to uncover the problem: These discrepancies between the published study and what was submitted to the FDA were discovered because the following information was available on the FDA web site: study protocol, FDA reviewer's comments, detailed information on trial outcomes.

Health Canada SBDs: The study protocol and the reviewer's comments are not included. Results of the individual studies (efficacy results and side effects) are not presented. Therefore, based on the SBDs it would also be difficult to determine if published studies combined the results of more than one clinical trial or if interim trial results are falsely presented as full trial results.

Conclusion: Most of the problems with the published study on celecoxib would not have been found through using the SBD.

b. Antidepressants

1. Efficacy of Antidepressants Compared to Placebo

Kirsch and colleagues analyzed efficacy data submitted to the FDA for approval of the six most

widely prescribed antidepressants approved between 1987 and 1999 (fluoxetin, paroxetine, sertraline, venlafaxine, nefazodone and citalopram). They showed that 80% of the response to medication was duplicated in placebo control groups and the mean difference between drug and placebo on the Hamilton Depression ScaleI was of questionable clinical significance. Placebo controlled trials of antidepressants are based on the assumption that drug and placebo effects are additive, that is, the drug is deemed effective only if the response to it is significantly greater than the response to placebo, and the magnitude of the drug effect is assumed to be the difference between the response to drug and the placebo. The conclusion of this study was that if the effects are additive then the pharmacological effects of these antidepressants is negligible. If the effects are not additive, alternative experimental designs are needed for the evaluation of antidepressants.

Information necessary to uncover the problem: In order to be able to evaluate the efficacy of each of the antidepressants versus placebo it was necessary to have the data on the results of each individual phase III (large clinical) trial submitted by manufacturers to obtain market approval.

Health Canada SBDs: This information is not available.

Conclusion: The conclusion that either these six antidepressants are no more efficacious than placebo or that trial designs need to be modified would not have been possible to make based on data in the SBDs.

2. Selective Serotonin Reuptake Inhibitors for Major Depression

A 2003 study published in the BMJ (British Medical Journal) looked at 42 placebo controlled studies of five SSRI antidepressants that were submitted to the Swedish drug regulatory authority between 1989 and 1994 as a basis for marketing approval for treating major depression. These 42 studies were compared with the ones that were eventually published. The authors found three types of biases:

Multiple publication: 21 studies contributed to at least two publications each, and three studies contributed to five publications.

Selective publication: studies showing significant effects of drug were published as stand alone publications more often than studies with non-significant results.

Selective reporting: many publications ignored the results of intention to treat analyses and reported the more favourable per protocol analyses only.

All of these biases resulted in a more favourable opinion of the drug and could have significantly affected the results of systematic reviews and meta-analyses.

Information necessary to uncover the problem: These biases were discovered because the authors had enough information to be able to compare published studies with those submitted to the regulator, including details of methods and results of each individual study submitted to the manufacturer.

Health Canada SBDs: The information available in the SBDs includes study number, drug doses, types of comparators and doses, number of patients (it is unclear if this is number screened, number enrolled or number analyzed) and duration of the trial. Results (efficacy and side effects) are not presented individually.

Conclusion: The biases between the submitted trials and the eventual publications would not have been discovered using the SBDs.

c. Cardiovascular Risks of Hormone Replacement Therapy (HRT)

The publication of the results of the Women's Health Initiative (WHI) showed that use of estrogen and progestin in postmenopausal women lead to increased cardiovascular risks. However, a combination of published and unpublished data submitted to regulatory authorities could have

uncovered these risks earlier making the WHI unnecessary. In 1997 Hemminki and colleagues took data on cardiovascular and cancer events from published randomized controlled trials on HRT and showed that odds ratio for cardiovascular and thromboembolic (blood clots) events for women taking HRT versus those not taking it was 1.97 (95% CI, 0.65, 4.21). In a second analysis, Hemminki added results from unpublished trials and although the overall results did not change significantly (odds ratio 1.97, 95% CI, 0.84, 4.63) the additional data hinted at publication bias as the relative risk in the unpublished trials was about 4.25 for cardiovascular events. McPherson and Hemminki have concluded that "systematic synthesis of all data from well conducted small clinical (efficacy) trials would have revealed the effect of hormone replacement therapy on cardiovascular risk much earlier, even than 1997 . . . [but] many of the studies were unavailable".

Information necessary to uncover the problem: In order to be able to add data from the unpublished trials to the meta-analysis the authors needed outcome and safety data on each individual unpublished trial.

Health Canada SBDs: This information is not available.

Conclusion: It would not have been possible to find the negative risk-benefit ratio for combined HRT in postmenopausal women based on data in the SBDs.

VII: Is the Summary Basis of Decision Adequate

IN EACH OF THE FOUR EXAMPLES the problems would not have been discovered using Health Canada's SBDs due to the lack of detailed information of various types in these documents. In each case, the necessary information includes a detailed report of the methods and results of each clinical trial submitted by the manufacturer. Such reports should include study design (including numbers of centers and countries in which they were located), an identification number, inclusion and exclusion criteria for patients, analytical methods, numbers of patients screened, enrolled, followed, and withdrawn (including reasons for withdrawals) and details of study outcomes including serious and total adverse events as well as efficacy outcomes.

A model for the minimum level of reporting already exists in FDA approval packages.

Once a drug has been approved in the United States the FDA posts on its web site a detailed summary of the information that the company has submitted, including the clinical trial data. The Table compares the extent to which clinical information is reported in the two sample SBDs for rosuvastatin (Crestor) and agalsidase beta (Fabrazyme) to the information on the FDA website. It is clear that compared to the U.S. what is available in Canada is grossly inadequate. There is no justification for Canada not matching the U.S. standard.

In order to be able to evaluate the thoroughness of the review process more than just the data that the companies submit is needed. It is also crucial to be able to see how the reviewers assessed that data, in-other-words, to have the reports from the reviewers. This additional level of information allows independent experts to understand what cri-

Comparison of Information Provided in Summary Basis of Decision (SBD) as compared to U.S. FDA Approval Packages

Is the following information included?	Sample SBD for rosuvastatin (Crestor)	Sample SBD for agalsidase beta (Fabrazyme)	US FDA approval package
List of individual Phase III trials [with ID number]	Yes	No ID's, but there was only one phase III trial	Yes
Details on each study protocol, linked to study ID	No	No	Yes
Results (linked to study ID):			
· Numbers of participants, baseline characteristics, withdrawals, follow-up	No [# of participants per study in total only; not per treatment arm]	No [# participants screened & randomized in total; not per treatment arm]	Yes
· Primary and secondary efficacy outcomes (number and percent per treatment arm; differences; tests of statistical significance)	No	No	Yes
· Fatal and non-fatal serious adverse events (number & type per treatment arm); total adverse events, withdrawals due to adverse events	No	No	Yes

teria were used in making risk-benefit decisions andwhere there might be potential weaknesses in the analyses that were done by the regulators. This type of information is also part of the FDA approval package and comments from Canadian reviewers should be publicly available here.

In June 2004, Health Canada held a multistakeholder meeting to discuss the progress that had been made on the SBDs and proposed implementation steps. When officials were confronted with the limitations of the SBD they defended the proposal by noting that this was only phase one of a proposed three phase model and that even the current model for the SBDs was open to modification based, at least in part, on what was heard in the meeting. Subsequent phases would examine the interpretation of the term "confidential information" and "*may* [emphasis added] see the inclusion of additional information" and "disclosure of negative outcomes or withdrawals [refusals to approve new drugs or new indications for older drugs, companies withdrawing submissions before a decision has been made] would be *explored* [emphasis added]". There are intimations of more to come but their exact form is deliberately being kept vague. Health Canada's explanation for the vagueness is that this is a new venture and each step needs to be carefully evaluated.

At the June consultation, this rational was not accepted by a number of organizations including the Alliance of Seniors to Protect Canada's Social Program, Canadian Treatment Action Council, Canadian Women's Health Network and Women and Health Protection. These groups drafted a statement explicitly outlining additional commitments that Health Canada would have to make before they would endorse the process. Among the elements that would have to be added to the proposal were: the use of expert advisory groups to review new drug applications, providing information about drugs that were not approved, posting adverse drug reaction reports (with patient identifying information removed) on the Health Canada web site, providing links to post-marketing information from other jurisdictions and ensuring that consumer and patient groups have adequate resources to be able to continue to participate in any further transparency initiatives (See Appendix 1).

VIII. Going Beyond Disclosure of Safety and Efficacy Information for Approved Drugs

THE DISCLOSURE OF CLINICAL INFORMATION is a key component to increasing transparency but there are further steps that must be taken to establish confidence in the drug regulatory system and to ensure that drugs are prescribed and used in an optimal manner. The Health Canada discussion document on new health protection legislation asks if there should be an opportunity for the public to present written comments about new products prior to their approval and whether there should be public hearings "where considered appropriate by the Minister". The Science Advisory Board's Committee didn't question if public hearings should be held but rather felt they were "desirable" although the Committee did go on to say that public hearings by themselves would not provide a sufficient level of transparency. The FDA provides an example of the use of open hearings. About 30% of new drug applications made in the United States go to advisory committee hearings. These hearings are both videotaped and also broadcast on the internet. At these hearings the company wishing to market the product defends its application; the advisory committee appointed by the FDA questions the applicant, sometimes with the help of external experts; and the general public has the opportunity to present facts or arguments deemed relevant to the application. Both the companies and the FDA prepare material for the advisory committee members that covers safety and efficacy of the new product and all of that information is also made available on the FDA web site. These meetings provide an opportunity for open public debate on the merits of new drugs before they are marketed.

The FDA committee system is not ideal. There are reports that some of the experts who sit on these committees have conflicts of interest. The House of Representatives Government Reform Committee has investigated allegations that certain physicians with multiple ties to heart drug manufacturers have been retained on the Cardiovascular and Renal Drugs Committee for extended periods in defiance of FDA regulations. An analysis by the newspaper USA Today found that more than half of the experts who served on FDA advisory committees from January 1, 1998, to June 30, 2000 declared potential financial conflicts with the drug or policy being discussed or voted on. The federal agency is forbidden from using experts with financial conflicts unless a waiver is granted, usually on the grounds that the experts' value outweighs the seriousness of the conflict. The FDA grants these waivers routinely. If Canada adopts a system of public hearings with expert advisory panels a strict system of screening for conflict-of-interest will be necessary.

Finally, just having data on drugs that have been approved is not enough. It is also important to know about new drugs and new indications for already marketed drugs that were either not approved or had their applications withdrawn by the companies. New drugs not approved might be chemically related to products already on the market and reasons for their rejection might point to unrecognized safety issues with the drugs that are available. Companies might resubmit applications for new drugs and in these cases it is necessary to know why the drugs were initially turned down to

be able to see if the deficiencies have been corrected. One such product on the Canadian market is Diane-35 an oral contraceptive that is marketed as a second-line agent for acne in women. This drug was rejected by the TPD twice, in 1993 and 1996, before finally being approved Drugs are often used off-label, for uses that were never approved by the regulatory authority. It may be that the companies have applied for use for the indication in question but been refused for either reasons of safety or effectiveness. Without knowing about the failed application doctors will continue to prescribe and patients will continue to take a product that may either be harmful in that particular situation or ineffective.

VIII. Summary of Recommendations

1. A detailed summary of all clinical information that companies submit as part of the regulatory approval process should be routinely posted on the TPD web site along with the reports from TPD reviewers.

2. Applications for approvals should routinely be sent to expert advisory committees for examination. Hearings of these committees should be public, interested members of the public should receive whatever information the committee members are given and there should be an opportunity for members of the public to make a statement to the committee.

3. There should be rigorous standards of conflict-of-interest for members of expert committees.

4. Clinical information and reviewers' reports should be available for new drugs and new indications for old drugs where their applications were refused or where the company withdrew the application.

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Appendix 1

Conditions for Endorsement of Summary Basis of Decision

GROUPS AND INDIVIDUALS SIGNATORY to the letter recognize and appreciate the strides made to date by the Health Products and Food Branch in creating an environment of consumer involvement and transparency. However, as it currently stands, the model for a Summary Basis of Decision put forward at this consultation does not meet these common goals.

We therefore recommend the following amendments and additions to this process:

1. Public hearings of expert advisory groups which discuss regulatory decisions. Individuals and organizations should be able to make submissions to these meetings, and the full materials disseminated to the committee and transcripts of hearings also publicly available (at the meeting and posted on the web). A process for determining the model for such hearings should be held with consumers organizations;

2. The full drug review should be posted on the web when a new drug is approved, including full reports of all chemical, pre-clinical and clinical studies submitted to the regulatory agency, reviewers' comments, and any conditions of approval (redaction by Health Canada only of information that could compromise individual privacy and commercial confidentiality to a level currently in place at the US FDA);

3. The history of the drug and approval process should also be posted on the web, including rejections of market applications, and any of Health Canada's decisions prior to a company's withdrawal of an application;

4. Product Monographs should be posted on the web, including patient product monographs, and all existing product monographs for currently approved drugs (previous versions plus latest revised version with date);

5. Adverse drug reaction reports should be posted on the Health Canada website in a format that is readily accessible and searchable by the public (reports submitted by the public, health professionals and manufacturers), as well as linkages to international governmental databases of adverse drug reaction reports;

6. Links should be provided to post-market information from other jurisdictions and results of new clinical trials carried out in the post-approval period;

7. In order for consumer and patient groups to participate effectively in any advisory or consultation process, there is a need for adequate resources to be provided for capacity-building, including training, internal consultation, and travel and accommodation.

Appendix 2

Statement of the International Working Group on Transparency and Accountability in Drug Regulation

1. Introduction

Health Action International (HAI)-Europe and the Dag Hammarskjoeld Foundation jointly convened an International Working Group to seek ways of promoting openness and accountability in drug regulation, both in industrialised and developing countries. The Working Group met in Uppsala, Sweden from 11-14 September 1996.

In recent decades, most countries of the world have established agencies to ensure the efficacy, safety and quality of pharmaceuticals, the validity of information relating to them, and to monitor patterns of utilisation and matters relating to rational use. These agencies must be regarded as servants of the public, acting to protect and advance health where drugs are concerned.

The regulatory agencies have assumed major responsibilities and large amounts of drug information are entrusted to them; the agencies themselves also generate policies, procedures and decisions. The scientific community and the public need this material but much of it is not available to them. It is needed both to ensure the effective and safe use of drugs, and to guarantee accountability, i.e. to provide a sound basis for scrutinising the activities of these agencies so as to ensure that they are acting efficiently and honestly in the public interest.

In recent years, freedom of information has become an increasingly accepted principle in democratic societies; many national governments subscribe to it, as do the European Commission and the World Health Organization. The principle of openness applies to pharmaceuticals as it does in other matters - often even more so because of the direct importance of drugs to people's health.

For these reasons, the Working Group set out to consider how essential information could be mobilised from drug regulatory agencies and their associated bodies without injuring any valid interest.

2. The origins of confidentiality in drug regulation

Most regulatory agencies and similar bodies have been established by law, and specific clauses in these laws usually require that they handle certain data confidentially. In addition, the employees of agencies are commonly bound by oaths binding upon civil servants requiring them to maintain secrecy on matters entrusted to them.

Two main arguments originally underlay the principle of regulatory secrecy in the drug field: First, it was considered that a commercial company which had used creativity and funding to devise and develop a drug could only reap a proper reward and fund future research by protecting it from immediate imitation by others. While patent law would protect certain matters, others could be protected only by maintaining secrecy.

Second, it was realized that information relating to individual persons (for example those participating in a drug research project or those in

whom adverse reactions had been reported by physicians) would have to be dealt with having full regard for personal integrity.

These principles need not be questioned but they need to be more fully defined. On which matters does the need for secrecy really outweigh the general need for openness? Where is the dividing line between legitimate trade secrets and "commercially sensitive" data? How do secrecy clauses in the law need to be changed?

3. Development of excessive secrecy

Drug agencies and inspectorates often maintain secrecy to a much greater extent than law or logic actually demand. Some laws, for example, only strictly require secrecy as regards personal data and the method of preparation of a drug, yet one often sees that no part of a regulatory file is accessible, and that reports about adverse reactions or poor manufacturing standards are sealed.

Various reasons underlie excessive secrecy:

- **lack of legal obligation**: in some countries, the law establishing regulatory bodies does not impose on them any duty of providing information.
- **lack of clarity in the law**: agencies or their staff may consider it safer to apply confidential clauses broadly rather than narrowly.
- **lack of tradition**: many countries have no tradition of transparency in government.
- **lack of consistent policy**: particularly in some developing countries there are (very) frequent changes in regulatory staff and general policy matters such as the provision of information receive little attention.
- **absence of explicit routines**: within the agency, who is competent to release a particular type of information, to whom, and in what circumstances?
- **lack of capacity and resources**: particularly in underresourced regulatory agencies, the time required to process requests for information may in itself be a barrier.
- **paternalism**: the frequent belief that those outside of the agency do not need, could not cope with or would misinterpret the information.
- **embarrassment**: an agency may hesitate to make fully public those decisions which are poorly documented or internally contested, papers which reflect poorly upon the agency's performance, or matters on which it might be criticised for not yet having taken a decision.
- **industrial influence**: many companies clearly prefer that entire regulatory files be regarded as secret.
- **over-caution**: there may be an exaggerated fear of upsetting commercial susceptibilities.
- **bureaucratic habit and inertia**: in agencies which are not subject to critical and transparent review, habits can form which discourage exchange of information.

4. The benefits of openness of drug information

Full availability of information is essential if all parties involved in health care are to participate effectively. Openness facilitates adequate feedback, proper setting of priorities and development of trust. A culture of openness protects conscientious individuals working in organisations of all kinds.

Knowledge relating to all drugs evolves constantly, as do standards and expectations relating to them, their producers and health care providers. However thorough the investigations made before a drug is licensed and marketed, much more will be learned about its efficacy, proper use and risks once it is marketed and used on a much larger scale. Almost no new element of knowledge emerges suddenly; as a rule it begins with impressions, suspicions and hypotheses. Where these arise - for example in reports of possible serious side effects in the journals - all existing relevant information will need to be mobilised to verify or discount this evidence so that the truth can be established as quickly as possible. Much of the infor-

mation needed for that purpose, including data on both animal and human experience, is unpublished and lies only within the files of agencies. By using it, the truth can be established much more quickly than if one is reliant purely on published evidence.

5. Consequences of excessive secrecy in drug regulation

Where secrecy is excessive the benefits set out in Section 4 will be lost. The risks that arise include the following:

- if a substantial part of the information existing on drugs remains hidden within regulatory agencies, and sometimes fragmented between them, the development of knowledge will be impeded. This is particularly dangerous where suspicion arises of a hitherto unknown risk.
- malpractice can be hidden from view; legal discovery in the course of litigation has for example revealed cases of falsification or suppression of unfavourable data by certain companies, or submission of inconsistent files on the same drug to different agencies.
- secrecy facilitates the circulation and use of sub-standard drugs.
- where a drug is subject to negative findings, the failure of a drug agency to explain its conclusions or provide background data, can leave the way clear for the sometimes very different and emphatic account given from the manufacturer.
- in a climate of secrecy and mistrust, the public is unlikely to believe even accurate and meticulously prepared official statements—assuming that they cannot be taken at face value and that some relevant information has probably been withheld.
- the incomplete availability and irregular release of information promotes a climate in which suspicion is generated and in which sensational and poorly founded stories on drugs break in the popular press; their reliability cannot be checked and unnecessary panic can be caused.
- secrecy has consequences which can be wasteful and even inhumane; scientific work, e.g. in humans or animals, which has already been performed by one company but hidden within regulatory files, may be repeated unnecessarily.
- if drug utilisation data are not available irrational drug use may continue unrecognised and unchecked.
- if research is sponsored by companies, unfavourable or unclear results may be withheld or the research itself may be stopped.

6. Current trends

The Working Group noted several current trends which can affect the free availability of drug information, favourably or otherwise.

First, the move towards adoption of Freedom of Information legislation continues, though only a few countries have as yet taken this step and existing laws contain important exceptions.

The current trend towards semi-privatised, industry-financed rather than tax-financed drug regulation can increase the degree of industrial influence on the regulatory process. The industrial preference for a high degree of confidentiality is likely to be pressed strongly.

Consolidation of drug regulatory activities into regional and multinational agencies is increasing, and collaboration between certain agencies is growing. This does not in principle lessen the challenge of ensuring sufficient openness; large regional groupings can practice excessive secrecy as much as national bodies.

7. General principle: Freedom of Drug Information

In principle information available within regulatory agencies should befreely available to any party requesting it. This basic principle applies at least

as strongly here as in other fields of governmental activity, and exceptions to it must be defined restrictively. There must also be a right of appeal to an independent higher authority if the regulatory authorities initially refuse to disclose.

The Working Group further noted that:

- Availability of information must extend not only to data reaching the agency from the outside, but also to its own deliberations, conclusions and actions.
- Data should where possible be released with some indications as to what is fact and what is hypothesis, but the release of the basic facts must not be restricted or delayed in order to add such commentary.
- The provision of information should not only be passive; agencies should actively provide and publish information in the public interest wherever possible.

8. Valid exceptions to the principle of free drug information

The two most important exceptions that can reasonably be made to the principle that drug information must be freely accessible are as follows:

a. Protection of legitimate business interests

The protection of innovative products and processes is primarily the concern of patent law and not of drug law. However on certain issues patent protection cannot be obtained yet there may still be a valid interest in maintaining secrecy to protect an innovation (e.g. relating to a manufacturing or finishing process) from competition.

A feasible approach would be for a manufacturer, when submitting a file to an agency, to state, with reasons, which specific parts of the file are considered confidential and for what period. This specification would be made on a standard form allowing the authority to confer in confidence about the types of matters accepted as justified under this exception.

b. Protection of confidential personal information

Personal data which enter the files of regulatory agencies or adverse drug reaction agencies can include the identity of the individual patient or health professional (or sufficient information to enable him or her to be identified indirectly) as well as information on the illness from which the patient is suffering and the drug treatment received. Information which might lead to the identification of individual patients should not be released by an agency to any party. A feasible approach would be to ensure that all personal data entering an agency is coded in advance in such a way that the individual cannot be individually identified, even by the agency itself.

Other limited exceptions to the principle of openness can arise.

9. The need for transparency at the international level

There is an increasing trend to exchange data and views between national regulatory and adverse reaction monitoring agencies. One example is the International Conference on Harmonisation (ICH) which aims to harmonise regulatory requirements between the United States, Japan and the European Union. In time, this will also have a major impact on data handling by agencies in other regions.

To date, ICH has concentrated primarily on accelerating the process of new drug approvals; it has scarcely considered the problems of the developing world, monitoring of existing drugs, and the broader aspects of drug safety. Information on ICH activities has been presented in such a way that their full repercussions have not been widely recognised. There is little possibility for developing countries with their special needs to influence the ICH process, and a broader process of consultation and full accountability is lacking. Mechanisms to ensure transparency and access to information should be integrated into harmonised procedures.

The Working Group noted that, although the WHO International Centre for Adverse Reaction Monitoring has been able to provide an increasing degree of public access to the data which it holds, some of the countries contributing data object to the release of their own information through the Centre, even when aggregated with data received from other centres. It was considered that these countries should be urged to allow the public use of their data through the Centre so as to enhance the usefulness of this international database in generating and examining early signals of possible side effects. Conversely, agencies should be encouraged to make fuller use at the national level of the signals now provided by the Centre on matters of potential concern.

An important form of international exchange is that of certificates of good manufacturing practice issued by drug exporting countries under the WHO Certification Scheme by federal, national or provincial authorities. Unfortunately, the reliability of these certificates varied very greatly. The Scheme will not be of optimal value to importing countries until there is some means of checking that a certificate has indeed been issued on the basis of competent and independent inspection.

10. Continuing Commitment

Secrecy in medicine is a serious obstacle to the attainment of health, in the drug field as in others. The participants in this Working Group made a continuing commitment to promote the further development of openness in drug regulation. They will do this by continuing to publicise the issue, stimulating discussions on the problems surrounding secrecy in drug regulation, surveying current disclosure policies of regulatory agencies and promoting the development and implementation of freedom of information laws applicable to drug regulation. The International Working Group invites other committed groups and individuals working towards greater access to drug information such as drug regulators, consumer organisations, interested NGOs, theWorld Health Organization, health professionals and public health associations to join its effort and work together in an expanding network.

Uppsala, Sweden, 11-14 September 1996

Appendix 3

Abbreviations

BMJ	British Medical Journal
EMEA	European Medicines Evaluation Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
HPB	Health Protection Branch
HRT	hormone replacement therapy
ISDB	International Society of Drug Bulletins
JAMA	Journal of the American Medical Association
NDA	New Drug Application
NSAID	nonsteroidal anti-inflammatory drug
RCT	randomized controlled trial
Rx&D	Canada's Research-Based Pharmaceutical Companies
SAB	Science Advisory Board
SBD	Summary Basis of Decision
SSRI	selective serotonin reuptake inhibitor
TPD	Therapeutic Products Directorate
TPP	Therapeutic Products Programme
WHI	Women's Health Initiative