Regulation and the Pharmaceutical Industry

HARMONY IN DRUG REGULATION, BUT WHO'S CALLING THE TUNE? AN EXAMINATION OF REGULATORY HARMONIZATION IN HEALTH CANADA

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Harmonizing standards on drug regulation makes sense, but it must protect safety, ensure that only drugs that are truly effective are marketed, and protect a country's ability to act independently. The main driving force behind international harmonization is the International Conference on Harmonization (ICH). When it comes to safety, the ICH has been harmonizing to the lowest common denominator. Examples of harmonization indicate that industry priorities have influenced the direction that Health Canada has taken. Harmonization is also intimately tied in with the policy of smart regulation, changing regulations in a way that enhances the climate for investment. Canada has introduced user fees in concert with other countries, but there are concerns that these may compromise safety standards. When it comes to transparency, Health Canada has chosen to adopt the more restrictive European Union model rather than the more open process used by the United States. Finally, there are a number of areas in which Health Canada has chosen not to harmonize, and in each case the decision is in the direction of lower safety standards. Harmonization could be of benefit to Canada, but the evidence to date suggests that Health Canada been harmonizing down rather than up.

The world of pharmaceutical regulation is a complex place. All regulatory agencies in developed countries agree that before drugs are marketed, they should be safe relative to the condition for which they are going to be used, efficacious (they should work under ideal circumstances), and manufactured according to rigorous standards. How these criteria are put into practice has traditionally been subject to a range of national standards. Therefore, in theory at

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least, it makes sense to develop a common set of standards that can be applied across developed countries. Similarly, it seems reasonable for countries to draw on each other's strengths in regulation so that tasks are not unnecessarily duplicated. In Canada's case, our resources and capacity are limited compared with those of other leading regulatory authorities, such the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). For 2009, the FDA's budget for its human drugs and biologics programs was just under US$1.1 billion, and it employed 4,816 full-time equivalents (FTEs) (1, 2), compared with CAN$98 million and 1,040 FTEs for Health Canada (3). The EMA coordinates the scientific evaluation of applications and related work with the national competent authorities of the 27 member states in the European Union and has more than 4,500 experts listed in its database (4, 5).

The move to coordinate regulatory practices typically goes under the name of harmonization. Harmonization, if done properly, could be beneficial nationally and internationally, but it requires harmonization to standards that do not threaten safety standards, that ensure drugs that are marketed offer significant therapeutic advances, and that preserve the scientific ability for countries to act independently when necessary. This article briefly reviews the history of international harmonization and then focuses on its implementation in Canada, in particular looking at whether the three conditions outlined above have been observed.

INTERNATIONAL CONFERENCE ON HARMONIZATION

The main driving force behind international harmonization is the International Conference on Harmonization (ICH), an elite organization with only six voting members—the brand-name industry associations and the regulatory agencies from the European Union, Japan, and the United States. In addition, Canada, the European Free Trade Association, and the World Health Organization sit as observers. The secretariat for the ICH is housed in the Geneva headquarters of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). The ICH was born out of a series of bilateral meetings, first between the U.S. and Japanese regulators, and then the European and Japanese. At the same time, European drug companies were anxious about their access to the American market, the largest in the world. Against this backdrop, the IFPMA took responsibility for organizing a series of trilateral meetings that led to the birth of the ICH in 1990 (6). There are notable absences from the groups that are allowed to participate in the ICH process. "ICH does not include representatives from professional associations, patient or consumer advocacy groups, the governments or health authorities of developing countries, companies specialising in generic drugs, or from groups producing pharmacopoeias" (7).

The economics of the pharmaceutical industry dictate that profits need to be made during the period when drugs are on patent, before generic competition, with its price reductions and loss of market share, sets in. Therefore, any duplication in research efforts or holdups in the regulatory process because of national differences are very costly for the brand-name companies, as each day of delay can equal millions of dollars in lost sales. Interviews with senior industry officials conducted by Abraham and Reed (6) confirm that companies were concerned about the inconsistencies between national regulatory standards that produce "wasteful duplication in drug testing," which "[drives] up drug development costs and create[s] 'barriers to trade.'" From the industry's point of view, the ICH was set up to alleviate these problems. This industry view of the ICH's purpose is reflected on the organization's website and leaves no doubt that the objective of harmonization is to reduce costs and bring drugs to market faster: "Regulatory harmonisation offers many direct benefits to both regulatory authorities and the pharmaceutical industry with beneficial impact for the protection of public health. Key benefits include: preventing duplication of clinical trials in humans and minimising the use of animal testing without compromising safety and effectiveness; streamlining the regulatory assessment process for new drug applications; and reducing the development times and resources for drug development" (8).

The mention of safety and the protection of public health in the ICH's statement is the rationale used by the regulatory agencies to justify their participation. According to an informant at the IFPMA, interviewed by Abraham and Reed, "The main reason the regulators can justify the time, effort, and expense of getting involved in ICH, is the promise that new and better medicines on a better scientific basis will reach the patient earlier and universally" (6). As we will see later, this is also the motivation given by Health Canada for seeking greater harmonization. The problem is that although regulatory approval times have shortened significantly in many jurisdictions (9), there has not been an increase in the number of newer and better medications. According to a database maintained by the French drug bulletin *Prescrire International*, in the decade spanning 2000–2009, of nearly 1,000 new drugs (or new indications for older drugs) introduced onto the French market, only 2 could be considered a major therapeutic innovation in an area where no treatment was previously available, and another 18 were important therapeutic innovations but with limitations (10).

Some analysts of the ICH argue that it "has the potential to improve medical care by finding an appropriate balance among competing regulatory styles" and that "as a consensual regulatory streamlining process, it will also have great impact on . . . the authority of experts in Europe, the United States, and elsewhere" (11). Others are much more critical of the process and claim that the ICH has not enhanced drug safety. Abraham and Reed have specifically examined four sets of ICH guidelines: reporting of adverse drug reactions (ADRs), patient exposure and clinical risk assessment, carcinogenicity testing

and the risk to patients participating in clinical trials, and duration of toxicity testing in animals. Based on both documentary analysis and an extensive series of interviews, they concluded that "across the four areas of drug safety and risk assessment, which we have examined, there are two striking trends: the ICH process has consistently failed to take opportunities to harmonise regulatory standards upwards; and has consistently concentrated harmonization efforts on *lowering* regulatory standards. Risks to public health, therefore, are likely to increase" (6; emphasis in original). The ICH has also taken a laissez faire attitude toward how quickly adverse reactions should be reported to regulatory authorities. The ICH has argued that expedited reporting is generally not required for reactions that are expected or are not serious. However, not taking action on delayed reporting "undermines patient safety, because analysis of adverse events that were not initially attributed to the drug in question can reveal previously unknown adverse reactions. Examples include the increased suicide risk associated with the so-called [antidepressant] 'selective' serotonin reuptake inhibitors, and the cardiovascular risks associated with rofecoxib [Vioxx]" (7).

HEALTH CANADA AND THE INTERNATIONAL CONFERENCE ON HARMONIZATION

Despite Health Canada's position as an observer at the ICH, there is surprisingly little general information available about Health Canada's role in the ICH on the department's website. (The ICH guidelines that Health Canada has adopted are available on the website.) There are only two relevant web pages. One page (www.hc-sc.gc.ca/dhp-mps/compli-conform/int/part/ich-cih_tc-tm-eng.php) has two short paragraphs, and the other (www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/index-eng.php) is not much better and occupies little more than a half-page of print.

A 1999 document from the Therapeutic Products Programme (TPP; the part of Health Canada that was then in charge of drug regulation) comments favorably on the ICH: "The TPP's participation in ICH is crucial as it is one of the most important international harmonization fora in drug regulation. . . . Since 1993, the TPP has adopted 16 ICH guidelines. Eighteen new guidelines are currently under development and will be adopted within the next few months" (12). At present, Health Canada "solicits comments on draft . . . guidances." Apparently this is done by posting the proposed guidances on its website, but unless someone knows specifically where to look, these are effectively hidden from the public (13). No other publicity is given to them, public meetings are not held to allow consumers and others to comment, and no analysis seems to have been done of their impact on the Canadian regulatory system.

HARMONIZING CANADA'S STANDARDS WITH THOSE OF OTHER COUNTRIES

As was previously noted, Canada has fewer resources to put into drug regulation than do other major players such as the European Union and the United States. Therefore, it could make sense for Canada to adopt standards consistent with those used by comparable countries. The pharmaceutical industry benefits from not having to repeat studies and from a reduction in paperwork, and Canadian reviewers can communicate more easily with their international colleagues when everyone is using the same set of data.

A 1999 document outlining the TPP's international strategy made it clear that the TPP saw pursuing international agreements as a priority. "Regulatory cooperation now means going beyond the exchange of information and personnel and is heading towards the sharing of issues, the development and implementation of cooperative and global solutions, and the establishment of cooperative mechanisms." At the same time, the document emphasized the need to maintain high safety standards. "The TPP must actively participate in and influence harmonization initiatives such as the development of international standards and guidelines to ensure that the high level of safety and quality standards currently applied in Canada are maintained or enhanced" (12). While Health Canada was emphasizing safety, at least on paper, in 1999 it was also consulting with the pharmaceutical industry about international regulatory cooperation. In those consultations, it was evident where industry's priorities lay (14). The drug companies saw the benefits of harmonization first in economic terms—faster market authorizations and reduced regulatory costs—and only secondarily as giving Canadians faster access to therapeutic products and high standards of safety and quality.

An early example of Canadian harmonization, and an example of how industry's economic priorities seemed to take precedence over Health Canada's concerns with safety, was the push to shorten the time taken to approve the first phase of clinical trials (15). Before any clinical trials of any type on experimental drugs (drugs that have never been marketed in Canada) can proceed, they must be approved by Health Canada. Up until January 2000, the TPP had a default time of 60 days to review applications for clinical trials. If it had not done so within that period, then the sponsor was free to proceed with the trial. In early 2000, the TPP proposed a change in the default time to 48 hours for Phase 1 studies. One of the main reasons offered for this change was that "the proposed option would provide the [pharmaceutical] industry with internationally competitive review times for the review of human clinical trial drug submissions" (16).

Echoing the rationale behind the ICH, the proposal claimed that the changes would result in increased access to improved therapy for the Canadian population. Despite this claim, in the analysis of the benefits and costs to the various

stakeholders, the first group to be considered was the pharmaceutical industry. What the TPP wanted to do was create conditions that would lead to the increased development of the pharmaceutical industry in Canada, as illustrated by the following statement in the report: "A number of firms claim to be interested in establishing facilities in Canada to conduct Phase I human clinical trials. However, it has been suggested that this can only be done if the Canadian regulatory system allows for a registration system for Phase I trials as well as reduced review times for other trials" (16).

The discussion paper put out by the TPP was deficient in a number of critical areas. The only mention of other countries' experience in the entire document was that these types of trials were not governed by legislation in the United Kingdom. The TPP did not offer any evidence that other countries had changed their review times or that an appropriate review could be conducted in 48 hours. After a series of consultations in which nearly all of the respondents opposed the 48-hour proposal, the TPP instead opted for a 30-day default review time (17).

Since that earlier change, Health Canada has gone on to sign a memorandum of understanding regarding therapeutic products with the United States (18), Australia (19), and most recently, the European Union (20). These memorandums allow an exchange of information between Canada and these countries, including position papers on future legislation and/or regulatory guidance documents, scientific advice on product development given to companies to promote innovation, assessments of applications for marketing authorizations, and information about the safety of marketed medicines to better protect public health (21). Of course, these exchanges are subject to confidentiality agreements, meaning that there will be little to no public access to the contents of the documents.

HARMONIZATION AND SMART REGULATION

The throne speech that opened the parliamentary session at the end of September 2002 enunciated a new direction in Canadian regulatory activities that entailed "speed[ing] up the regulatory process for drug approvals to ensure that Canadians have faster access to the safe drugs they need" (22). This move was part of a larger government initiative that goes under the rubric of "smart regulation." Smart regulation means that Canada should "regulate in a way that enhances the climate for investment and trust in the markets" and "accelerate reforms in key areas to promote health and sustainability, to contribute to innovation and economic growth, and to reduce the administrative burden on business" (22).

A couple of the key messages from smart regulation are highly relevant to drug regulation. The first is that Canadian standards should conform to those of its major trading partners. In the words of the Expert Advisory Committee (EAC) on Smart Regulation, "It requires the removal of regulatory impediments to an integrated North American market and the elimination of the tyranny of small differences. . . . In cases where regulatory differences are insignificant or

present low risk, it may be in the public interest for Canada to be pragmatic and simply align its approach with that of the United States. The Committee believes that the smart approach, in these cases, is to avoid unnecessary duplication and focus regulatory resources on situations that warrant a unique Canadian solution" (23). This position aligns very closely with the position taken by the pharmaceutical industry on whether Health Canada should adopt its own regulatory standards or use those from other countries. According to a spokesman for Canada's Research-based Pharmaceutical Companies (Rx&D), the brand-name-drug makers' association, "Unless Health Canada can show that an independent review process is essential to the health and safety of Canadians . . . why not piggyback [with the United States]?" (24). At a Health Canada meeting to discuss changes in the regulatory system regarding, among other things, licensing requirements, industry representatives asked "whether there have been discussions with the ICH to align our rules with theirs, as there may not be much value in setting entirely new and Canadian rules if there are already appropriate ones in place at ICH." At another point, when the discussion moved to post-marketing study commitments, industry encouraged Health Canada to use flexible and harmonized rules and advised against developing "Canadian only" rules (25). Of course, no one is directly talking about lowering safety standards, and in fact the EAC says safety is paramount. On the other hand, there is no explicit talk about harmonizing upward to the highest standards, just harmonizing. As we have already seen, in some cases the ICH process involves harmonizing to a lower standard.

The economic theme enunciated by the EAC was picked up and elaborated on by the federal government's Policy Research Initiative (PRI), a branch of the Privy Council Office in the federal government that is charged with carrying out medium-term, cross-cutting research projects (26). One of the key points made by the PRI was that if the decline in the Canadian regulatory burden had matched that of the United States over the 25-year period between 1979 and 2004, then investment in Canada could have been 30 percent higher than it was. Looking specifically at drug regulation, the PRI calculated that enhanced regulatory cooperation with the United States for new medications could mean a 10.5 percent increase in the value of sales, a gain in net income for the pharmaceutical companies of 6.6 percent, and a 4.2 percent higher rate of return. The PRI, citing mostly literature generated by Industry Canada, went on to dismiss concerns that more cooperation and collaboration with the United States would endanger health, safety, and the environment (27).

A second main area where smart regulation, as set forward by the EAC, highly affects drug regulation is around the timeliness of reviews of new drug applications. "The Committee decided to focus its recommendations on how international regulatory cooperation can improve Canadians' access to new drugs by speeding up the drug approval process" (23). The message is that Canadians are losing out because Health Canada is relatively slow in undertaking drug

reviews. Just as harmonization can help remove differences between Canadian and other countries' regulations, so the EAC believes that "increased international cooperation in the review of new drugs can lead to direct benefits for citizens in terms of accelerating the introduction of safe new therapeutic products to the Canadian market." Not surprisingly, review times are also a central focus of the brand-name pharmaceutical industry. In a 2002 document, Rx&D called for faster Canadian reviews and noted that "other measures to accelerate drug reviews and approvals require better international harmonization of standards with other countries" (28).

There is no argument against getting breakthrough drugs onto the market faster, but these represent less than 1 percent of all new drugs. On the other hand, there is highly suggestive research linking faster regulatory approval to increases in safety problems. Abraham and Davis compared drug withdrawals in the United Kingdom and the United States in the period 1971–1992 and reported a ratio of 2.67:1 (24:9 drugs). Their explanation for the lower number of withdrawals in the United States was that the longer period spent examining the data allowed U.S. regulators to detect serious safety problems before products were marketed (29). Estimates suggest that during the period 1990–1995, for every one month reduction in a drug's review time there was a 1 percent increase in expected reports of hospitalizations for ADRs and a 2 percent increase in expected reports of ADR-caused deaths (30).

HARMONIZATION AND COST RECOVERY

The principle behind cost recovery is that pharmaceutical companies financially benefit from the drug review process by virtue of being able to market their drugs, and therefore the companies should bear some of the cost of the review. Cost recovery in Canada started in fiscal year 1994–95 to compensate for a reduction in direct government funding, as the government sought to eliminate the budgetary deficit by cutting expenditures. Cost recovery was also seen as "a means of transferring some or all of the costs of a government activity from the general taxpayer to those who more directly benefit from or who 'trigger' that special activity" (31). Health Canada's spring 2010 proposal to update the fees it charges, subsequently approved by Parliament, draws on an international comparison to justify the new level of fees. In choosing Australia, the European Union, the United Kingdom, and the United States, Health Canada justified its selection "because of the similarity of their regulatory frameworks for therapeutic products to that in Canada, and [these countries] are thus considered to be 'comparable.' . . . Each jurisdiction has a similar fee-paying clientele. Many of the clients are multinational companies that market/manufacture in all five jurisdictions" (32).

Principal-agent theory proposes that there is a relationship between a principal who has a task that needs to be performed and an agent who is contracted to do the task in exchange for compensation. Before the introduction of user fees, the

principal was the Canadian public and the agent was Health Canada. However, since 1994 a new principal has been added: the pharmaceutical industry that is now providing a substantial fraction of the money needed to run the drug regulatory system.

The industry's new-found status as a source of funding creates tensions in the regulatory process that compromise the ability of agencies to properly evaluate new products. Abraham and Lewis (33) have pointed out that since most of the regulatory agencies in the E.U. countries are funded to a considerable extent by user fees, there is often intense competition for Rapporteur and Co-rapporteur status in order to generate income. (The Rapporteur and Co-rapporteur are the national regulatory agencies that actually do the evaluations of the new drug applications.) This competition puts the national agencies under considerable pressure to conform to, or better, the European Union's 210-day timeline for drug reviews, as companies look at the time taken to do reviews as one of their key criteria when recommending a Rapporteur and Co-rapporteur. Industry representatives interviewed by Abraham and Lewis did not regard this competition as a threat to public health, but of 15 E.U., German, Swedish, and U.K. regulators, 5 agreed that it was, and an additional 5 thought that it was possibly a threat (33). In a similar vein, a British House of Commons Committee looking into the influence of the pharmaceutical industry concluded that "the MHRA [Medicines and Healthcare products Regulatory Agency], like many regulatory organisations, is entirely funded by fees from those it regulates. However, unlike many regulators, it competes with other European agencies for fee income. This situation has led to concerns that it may lose sight of the need to protect and promote public health above all else as it seeks to win fee income from the companies. No evidence was submitted with proposals for a better system for funding the MHRA, but it is important to be aware of the dangers of the present arrangements" (34).

The U.S. FDA has a statutory requirement to complete its review of 90 percent of new drug applications within specific periods of time, depending on whether it is a standard or priority review. If the FDA fails to meet that obligation, then renewal of legislation that allows it to collect user fees from industry may be endangered. The conclusion reached by Carpenter and coworkers (35) was that when drugs are approved in the immediate pre-deadline period, there is a substantially higher rate of eventual drug withdrawals and/or safety labeling changes compared with drugs approved after the deadline. In other words, it appears that if the deadline is imminent, the FDA does a less thorough job of reviewing drugs in order to avoid crossing the deadline and potentially jeopardizing its revenue from drug companies.

Similarly, in Canada, revenue to the TPD will also suffer if service standards (completion of reviews of new drug applications within the targeted time) are not met. If the actual performance in a given fiscal year is more than 110 percent of the target for a particular fee category (different types of approval applications

are subject to different fees), penalties apply for the amount in excess. Fees are then reduced for the next reporting year by a percentage equivalent to the performance not achieved, up to a maximum of 50 percent; for example, if approvals are 20 percent over time, fees will drop by 20 percent (36). Faced with the prospect of penalties, it is possible that the TPD might follow the pattern set by the FDA and rush to approve new drugs that are approaching the deadline, to avoid incurring a financial loss in the next year.

HARMONIZATION AND TRANSPARENCY

Health Canada has long been criticized for treating clinical material on drug safety and efficacy submitted by pharmaceutical companies as confidential business secrets and refusing to release it unless the company submitting the information agrees. In 2000, its own Science Advisory Board 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" (37). A 2004 report from the House of Commons Standing Committee on Health echoed the Science Advisory Board: "The Committee does not support a clinical trial system that discourages openness in order to protect commercial interests. It feels that individual Canadians may be harmed by the lack of scrutiny and by a dearth of independently assessed information. It calls for increased transparency for Canadians and more accountability by Health Canada" (38). Health Canada's penchant for secrecy was recognized by the Canadian Association of Journalists, which gave the department its fourth annual "code of silence" award for being the most secretive government department in Canada, because of its "remarkable zeal in suppressing information" and "concealing vital data about dangerous drugs" (39).

In the face of all of this criticism, Health Canada could have chosen to harmonize its level of transparency with that of the FDA. About one-quarter to one-half of all the drugs being considered for approval by the FDA go to an advisory committee for hearings. Advisory committee meetings are held in public, all of the information being considered by the committee is publicly available, and there is a brief period at the start of the meeting for public comment. Furthermore, the FDA eventually posts on its website edited versions of the comments its reviewers have made about the clinical data submitted by drug companies. Instead of the FDA, Health Canada chose the European Public Assessment Reports (EPAR), documents released after a drug has been approved, as its model for enhanced transparency (40).

At the time when Health Canada was commenting favorably on the EPAR, others were not so positive. An analysis of nine EPARs issued between September 1996 and August 1997 found that there was no standardized method of presenting information in these documents. Examples of the problems included a

lack of consistency in whether or not the Scientific Discussion section contained an introduction and epidemiological data, and in whether or not the mechanism of action of the drug was fully described. Clear reporting of clinical trials was sometimes absent, and references to published trials were missing in all nine EPARs (41). A subsequent analysis that covered all EPARs published in 1999 and 2000 revealed that the EPARs were not harmonized, reliable, or correctly updated (42).

The Summary Basis of Decision, Health Canada's version of the EPAR, which it has been producing for the past five years, explains the scientific and benefit/risk information that the department considered in making its decision to approve a new medicine. These documents lack information about the study protocol, the baseline characteristics of trial participants, the number of participants who withdrew and reasons for their withdrawal, primary and secondary efficacy outcomes, and fatal and nonfatal serious ADRs, by treatment arm (43). Without this type of information, it is virtually impossible to independently assess the safety and efficacy of new products.

Finally, although the EMA announced that beginning in 2005 it would start publishing EPARs for drugs denied approval (44), Health Canada has not followed suit.

WHAT DOES NOT GET HARMONIZED

Health Canada views harmonization through a selective lens. Although, as we have seen, a number of aspects of drug regulation have been harmonized with those of other countries, other areas have been deliberately ignored.

No Harmonization on Releasing Information about Adverse Drug Reactions

There is no standard for the length of time between the receipt of an ADR report and when that ADR has been analyzed and posted on Health Canada's MedEffect Adverse Reaction Database. The United Kingdom commits to three to seven days to process ADR reports, and Australia targets initial professional review of ADR reports within three days. Health Canada has explicitly rejected developing comparable standards, claiming that "development of quantitative service standards for post-market surveillance activities or compliance and enforcement activities is difficult given the unpredictability and volatility of the activities involved" (32).

No Harmonization on Registering Clinical Trials

In recent years, a couple of high-profile scandals have led to a growing call for transparency in the results of clinical research. GlaxoSmithKline did not publish results that showed that paroxetine (Paxil) was ineffective for the

treatment of depression in children and adolescents, because, according to an internal company memo, "It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine" (45). The *Wall Street Journal* claimed that "internal Merck e-mails and marketing materials as well as interviews with outside scientists show that the company fought forcefully for years to keep safety concerns from destroying . . . [Vioxx's] commercial prospects" (46).

Since the end of 2007, the FDA has required drug companies to post a variety of data about clinical trials with at least one trial site in the United States on a publicly accessible registry, including the population being studied, the study design, outcome measures, and recruitment information. By the end of September 2008 this requirement was expanded to include reporting basic results within one year of completion of the trial, and by September 2010 more extended results needed to be posted (47).

Health Canada has been talking for more than five years about registering clinical trials done in Canada. There was a workshop on this topic in June 2005, an external working group met in April 2006, and in June–July 2006 people were given the opportunity to complete an on-line questionnaire on the topic (48). The external working group delivered its report in December 2006 (49). According to the Health Canada website, "Health Canada will consider the results of the public consultations and the External Working Group's recommendations before making a final decision on how to proceed with the registration and disclosure of clinical trial information in Canada" (50). No timeline or process is given for making the final decision. It should also be noted that initial industry reaction to the idea that Canada should require registration of clinical trials was negative. Speaking for Merck (51), Dr. Laurence Hirsch, its vice-president of medical communications, said: "Premature disclosure of proprietary information by Merck (or other companies) can result in significant competitive disadvantage and loss of incentive or reward for new product development. Hence we, like others, do not concur with calls for mandatory registration of all clinical trials at their inception."

No Harmonization on Patient Information Leaflets

When patients receive prescriptions in Canada, they may be presented with an information leaflet regarding the product they are going to be using. However, including these leaflets with each prescription is not mandatory, and the content of these leaflets is not approved by Health Canada. The leaflets are individually produced by commercial companies and, as such, the quality of the information varies from leaflet to leaflet (52, 53). In contrast, the Australian Therapeutic Goods Administration has required all prescriptions to have patient-information leaflets since 1993 (54), and the European Union's EMA has had a similar requirement since 1999 (55).

CONCLUSION

Once again, it is important to emphasize that regulatory harmonization could bring important benefits, but these benefits can only be recognized if Canada harmonizes up. The evidence to date suggests that harmonization has been to a lower standard. When faced with harmonizing to stronger standards in some jurisdictions, Health Canada has not gone in that direction. The various documents released by the supporters of harmonization have generally failed to look at the effects that harmonization might have on Canada's ability to take independent regulatory action. The PRI touched on this question when it asked whether Canadian sovereignty might be compromised by harmonization. It dichotomized the debate between "Canada's right to make sovereign decisions" and "the process and evidence used to make final, sovereign decisions," and answered that the latter was the most important, "that Canada's sovereignty is exercised through strategic policy decisions" (27). But what the PRI failed to take into account was that harmonization may lead to stripping away the intellectual and possibly the physical scientific resources necessary to make these strategic policy decisions. If Canada relies too much on the Americans or the Europeans to generate the information that it needs, or takes their decisions and "Canadianizes" them, then it runs the distinct risk of reducing Canada's overall level of expertise. Recall the mass exodus of Canadian aerospace expertise to the United States after the Diefenbaker government in the late 1950s decided that development of the Avro Arrow jet fighter was too expensive for Canada and that instead the country should rely on U.S.-built missiles and aircraft for defense (56).

Especially when it comes to harmonizing with the FDA, supporters also invariably fail to point out the highly political nature of the agency. The commissioner of the FDA is a presidential appointee, meaning that political ideology is potentially a very important factor in who gets the job. During the time that George W. Bush was president, the FDA repeatedly turned down requests to make the "morning after" pill an over-the-counter drug. These decisions ended up forcing the assistant FDA commissioner for women's health and director of the Office of Women's Health at the FDA to resign her job, citing her belief that the agency was "disregarding the scientific and clinical evidence and the established review process and [was] taking an action that harms women's health by denying them appropriate access to a product that can reduce the rate of unplanned pregnancies and the need for abortions" (57). How exactly would Health Canada deal with an FDA making decisions on religious rather than scientific grounds?

While the same concerns about politicization don't apply to the EMA, the E.U. agency is rife with conflicts of interest. In April 2008, of 2,127 experts (from a total of 4,528) included in its Expert Database who had up-to-date declarations of interest, more than one in four had "high risk" conflict of interest. Twenty-five percent of the members of the Management Board declared interests

in the pharmaceutical industry (5). How exactly would Health Canada deal with decisions made by a conflicted EMA?

The evolution of drug regulation in the European Union provides a lesson in the difficulties associated with accepting regulatory harmonization. The initial attempt was known as "mutual recognition," whereby companies were encouraged to seek simultaneous marketing authorization for a drug in five or more member states, provided that they already had market authorization in at least one country. However, if other states dissented from the original authorization decision, they could seek arbitration. Before the system was changed in 1995, countries raised objections to all but one of the 300 applications that were submitted, indicating a very strong reluctance to accept the findings of another regulatory agency (33). Even after a 1995 reform to the system and more than 20 years of regulatory harmonization, 7 of 15 European regulators thought that harmonization was likely to lead to a leveling down of safety standards, with an additional 2 regulators uncertain (33).

Finally, the ideology behind harmonization is that it is all about establishing the same technical requirements for regulatory agencies. However, drug regulation is more than just technical specifications. As Daemmrich (11) points out, regulatory frameworks are a reflection of the therapeutic culture that has developed in an individual country. These "therapeutic cultures arise from networks of actors that produce regulatory policy, determine testing standards, and ultimately decide on market access for new drugs. The principal actors in medical policy (regulatory agencies, physicians, pharmaceutical companies, disease-based organizations) form a rather fluid and flexible network that sustains intense debates and very serious differences of opinion." It would be a serious mistake to think that national networks are the same across different countries. It misses the point that drug regulation is the intersection between values, science, medical culture, patients' needs and expectations, and politics. Abraham and Davis (58) concretely illustrate this point with their evaluation of the differences in regulation of nonsteroidal anti-inflammatory drugs in the United States and the United Kingdom. Harmonization has to respect these national differences and not treat individual country systems as if they are interchangeable.

More harmonization might stimulate more economic activity in the pharmaceutical industry, but at what price in terms of safety? Some of the guidances brought out by the ICH and adopted by Health Canada have used the lowest common denominator as the standard for safety. Harmonizing with other countries on user fees and review times also has the potential to increase safety problems. This possibility is especially troubling as an ever increasing number of people are exposed to new drugs that eventually have to be withdrawn because of safety concerns (3). The claims that harmonization will lead to faster access to newer and better drugs simply don't stand up to the facts, which show that only a small fraction of new drugs represent major therapeutic advances.

Regulatory harmonization needs to be undertaken in the interests of public health. To date, that has not been happening.

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