More than 80 percent of clinical drug trials in Canada are funded by the pharmaceutical industry. This article evaluates the overall state of clinical trials in Canada and looks at the interplay between public and private interests. Health Canada has adopted standards developed by the International Conference on Harmonization, a body that is heavily influenced by industry. Commercial interests are increasingly involved in recruiting patients into clinical trials and in running these trials. It is in industry’s interests to conduct drug tests on people for which it is easiest to see benefits. These interests are not fundamentally challenged by Health Canada’s policy of issuing nonmandatory guidelines on who should and should not be included in clinical trials. The outcome of clinical trials is heavily influenced by commercial sponsorship, with the result that trials may favor corporate interests rather than the interests of the public. How Health Canada deals with that possibility is not known, because of its strict policy of treating clinical trial data as private property. If clinical trials are to serve the purpose for which they are designed, developing reliable and objective information about new drugs, then commercial interests cannot be allowed to take precedence over health interests.
starting with examining the pharmacological action and toxicity testing in small groups of healthy people (Phase I) and building to studies in hundreds to thousands of people with the disease that the drug is designed to treat, diagnose, or prevent (Phases II and III) (7) (Table 3). The objective of the trials is to prove the efficacy of the product—that is, whether or not it works under ideal circumstances—and prove that it has an acceptable safety profile. Although trials done in other countries can be used in applications to market drugs in Canada, Canada is an attractive place to conduct trials because of its public Medicare system, the large numbers of highly trained scientific personnel, the high quality of the data generated, its proximity to the United States, and lower costs than in the United States (8, 9).

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Amount spent by industry, Canadian $ millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>567.1</td>
</tr>
<tr>
<td>2004</td>
<td>501.9</td>
</tr>
<tr>
<td>2003</td>
<td>487.5</td>
</tr>
<tr>
<td>2002</td>
<td>442.8</td>
</tr>
<tr>
<td>2001</td>
<td>445.8</td>
</tr>
<tr>
<td>2000</td>
<td>425.7</td>
</tr>
</tbody>
</table>

Source: Patented Medicine Prices Review Board (3–5).

Table 2

<table>
<thead>
<tr>
<th>Type</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical</td>
<td>771</td>
<td>1,287</td>
<td>1,484</td>
<td>1,730</td>
<td>1,740</td>
<td>1,686</td>
</tr>
<tr>
<td>Biological</td>
<td>54</td>
<td>180</td>
<td>211</td>
<td>258</td>
<td>239</td>
<td>272</td>
</tr>
<tr>
<td>Total</td>
<td>825</td>
<td>1,467</td>
<td>1,695</td>
<td>1,988</td>
<td>1,979</td>
<td>1,938</td>
</tr>
</tbody>
</table>

Source: Health Products and Food Branch, Health Canada (6).
<table>
<thead>
<tr>
<th>Phase</th>
<th>Purpose</th>
<th>No. of trial participants</th>
<th>Type of trial participants</th>
<th>Length of time, years</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Determine pharmacological actions of the drug and side effects associated with increasing doses</td>
<td>20–50</td>
<td>Healthy people</td>
<td>1</td>
<td>Drug has never been administered to humans before; safety information is based on actions of drug and animal testing</td>
</tr>
<tr>
<td>II</td>
<td>Evaluate efficacy of the drug; determine side effects and risks</td>
<td>100–300</td>
<td>People with medical condition to be treated, diagnosed, or prevented</td>
<td>2</td>
<td>Wider group of patients exposed; disease in question may alter the drug’s action, leading to unexpected side effects</td>
</tr>
<tr>
<td>III</td>
<td>Gather the additional information about efficacy and safety needed for further risk-benefit assessment of the drug</td>
<td>Several hundred to several thousand</td>
<td>People with medical condition to be treated, diagnosed, or prevented</td>
<td>3+</td>
<td>Wider group of patients exposed; drug administered for longer periods of time; disease in question may alter the drug’s action, leading to unexpected side effects</td>
</tr>
</tbody>
</table>

Sources: Government of Canada (12) and Hawthorne (62).
Both federal and provincial governments are eager to increase the number of clinical trials being conducted in Canada, for a variety of reasons including helping Canada to achieve a knowledge economy, helping to provide an environment that encourages Canadian-trained researchers to remain in the country, and providing Canadian health professionals with early access to new medications to improve medical treatments. To achieve these goals governments have structured the federal-provincial corporate income tax system into one of the most favorable systems in the world in its treatment of research and development (10). Although these incentives apply to all research and development done in Canada, over the past decade “successive governments and regional agencies have worked hard to convince global companies that Canada has the right infrastructure and conditions to promote innovation and encourage new drug development” (11). Industry Canada has produced promotional documents encouraging companies to use Canada for their clinical trials (9).

This article draws on a disparate body of literature in a preliminary effort at evaluating the overall state of clinical trials in Canada, in particular examining the interplay between private and public interests in how the conduct of clinical trials is regulated. As part of the federal government’s strategy to increase the number of clinical trials in Canada it changed the rules on how quickly it would provide approval for these trials to begin. An analysis of this decision forms the starting point for this article. I then discuss how, in an effort to harmonize Canadian requirements for clinical trials with those in other major countries, Health Canada has adopted guidelines put out by the International Conference on Harmonization, guidelines that may not always prioritize safety. The article then looks at the Research Ethics Boards that have to approve any clinical trial before it can start, and at how companies go about recruiting doctors and patients for trials and which groups are not explicitly included. Increasingly, all aspects of the running of clinical trials are being commercialized, and I discuss how this affects the ethical and scientific standards of trials and how Health Canada monitors ongoing trials. The article then considers how the trials are analyzed and what Health Canada does with the data. In the wake of several scandals there has been a rising chorus of calls for all clinical trials to be registered. Health Canada has held stakeholder forums on this topic and I look at the progress on this to date. Finally, I draw out some themes that are common to all aspects of this issue and look at whether the current enthusiasm for increasing the number of clinical trials in Canada has been tempered with a regulatory system that is adequate to ensure public safety.

CHANGING THE RULES FOR CLINICAL TRIALS

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
Until January 2000, the Therapeutic Products Programme (TPP), now known as the Therapeutic Products Directorate (TPD), the branch of Health Canada dealing with prescription and nonprescription drugs, 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 changing 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” (12).

In looking at changes to review times, the TPP made clear that it was only advancing options that would not hinder trade. Safety was mentioned but seemed to take a back seat to economic considerations. 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 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” (12).

While it may or may not be a reasonable objective to promote the interests of the pharmaceutical industry, this was not the mandate of the TPP. The mandate of the TPP was to ensure that Canadians had access to safe and effective drugs. It is in this light that any changes need to be evaluated.

The initial 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. Dr. Charles Weijer, a bioethicist at Dalhousie University, said “this [proposed change] causes me grave concern. One has to be very careful about getting into a competition for clinical trial revenues that’s based on having the lowest ethical standards” (13).

The proposal also claimed that the changes would result in increased access to improved therapy for the Canadian population. This claim was a serious misreading of the nature of clinical trials. Most of these trials are randomized studies in which, by definition, half of the participants receive either a placebo or standard therapy. Moreover, the very essence of a clinical trial is that it is unknown whether the new therapy is better than, worse than, or the same as

---

1 Clinical trials for new indications for drugs already marketed must also be approved by Health Canada.
existing, standard therapy. In fact, most new therapies are moderately, little, or no better than existing treatments and therefore do not offer any additional benefits to trial participants. Speeding up the exposure to new drugs rarely equates with better health outcomes, despite the explicit statement in the TPP proposal.

The TPP reported that almost all of the 80 respondents to its consultation process objected to the 48-hour period, and in the end the TPP opted for a 30-day default review time (14). In the summer of 2006 an electronic survey of stakeholders asked their opinions of the changes to clinical trial regulations made in 2001. Between two-thirds and three-quarters of the stakeholders indicated strong support for the statements that the following objectives have been met: improving safety mechanisms for clinical trial subjects, shortening review times, ensuring a flexible framework with sufficient safeguards to ensure the review of clinical trial applications is not unduly delayed, and improving monitoring and follow-up by the regulator (6). At the same time the Auditor General documented that drug program managers thought their regulatory activities were insufficient to meet the regulatory requirements in the area of monitoring the safety of drugs already on the market (15). Whether or not they have sufficient resources to adequately evaluate clinical trial proposals has not been investigated. Furthermore, there has not been any objective study of the quality of the reviews since the change to a 30-day default review.

**HARMONIZING STANDARDS**

In theory it makes 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 working from the same page. A 1999 document outlining the TPP’s international strategy made clear that it 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” (16). 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” (16).

The main organization responsible for standardizing procedures for clinical trials is the International Conference on Harmonization (ICH). The ICH is in charge of a process that has been underway since 1990 to harmonize the regulatory requirements for drug approval in the world’s major markets. The main players are the industry associations from the United States, European Union, and Japan.
along with the regulatory agencies in these countries. Representatives from the World Health Organization, the European Free Trade Area, and Canada have “observer” status at ICH meetings.

John Abraham and Tim Reed (17) at the University of Sussex have studied the ICH in detail and in their view, within the ICH process, the main knowledge flow has been from industry to regulators, with industry tending to set the agenda. There has been no participation by consumer/patient organizations, academics, health care professionals, or the generic drug industry. Therefore, the sources of expertise framing innovations on which kinds of tests are necessary before registering a new drug have been narrowly based. Abraham and Reed note that a further consequence of the lack of challenge to an industrial agenda is the weak commitment to product innovation in the public interest (17).

Abraham and Reed have specifically examined four sets of ICH guidelines—reporting of adverse drug reactions, patient exposure and clinical risk assessment, carcinogenicity testing and the risk to patients on 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” (18, emphasis in original).

Canada has adopted nearly all of the ICH guidelines. Although the ones being considered are posted on the Health Canada website for consultation, they receive no other publicity, public meetings are not held to allow consumers and others to comment, and there seems to have been no analysis of the impact on the Canadian regulatory system.

RESEARCH ETHICS BOARDS

Before clinical trials can go ahead in Canada they need to be approved by ethical committees known as Research Ethics Boards (REBs). All hospitals where research is conducted have REBs, as do universities. Currently, there are some 300 local REBs (19). The regulations of the Food and Drugs Act set out the minimum membership for REBs but are silent on the procedures that these boards should follow and the standards that should govern their operations (20). Canada has no accreditation or inspection system for REBs, and as of 2002 had no oversight mechanism for the way they undertake their reviews (19). “The TPD requires sponsors of clinical trials to submit a ‘Research Ethics Board Attestation’ with their request to conduct a clinical trial involving a New Investigational Drug. Their attestation must be signed by the chair of an REB and kept on file by the trial sponsor for 25 years. Aside from identifying information on the REB and its chair, no further information about the REB or its review is required” (21).
Members of publicly based REBs, the ones in universities and hospitals, have expressed unease about the relationship of the boards with the pharmaceutical industry. A report on the governance of human research from the Law Commission of Canada quotes some REB members on this subject: “We have more trouble with some of the commercial protocols because we worry that their motives may be different than the motives of a cooperative study group.” “In terms of the shift to industry-sponsored research, I see the conflicts of interests that are arising at a exponential rate” (22). The commission report concludes that given the industry funding of such a large proportion of research, the institutions where this research is based are becoming financially beholden to companies whose primary goal is profit not science and the generation of knowledge (22).

Perceived delays with REBs in academic institutions have led companies to move their trials out of hospitals and universities into the community setting. Between 1997 and 2004 the percentage of trials in the community rose by 13 to 60 percent of the total (2). In this setting there are no public REBs, except in Alberta where the College of Physicians and Surgeons of Alberta has set up a REB to review community-based trials (2). Elsewhere in the country these community trials will be reviewed by for-profit REBs that receive a fee for their work from the organization that is sponsoring the trial, in nearly all cases a pharmaceutical company (23).

Trudo Lemmens, who teaches at the University of Toronto Faculty of Law, has written extensively with his colleagues about for-profit REBs. He believes that the credibility and integrity of the research review are compromised by the perception of a possible conflict of interest when commercial REBs approve a clinical trial. If the REB turns down too many trials or demands costly changes to the research protocol, companies may be reluctant to continue to use it. In Lemmens’s opinion the honesty of individual REB members is not enough to remedy this situation (24).

The main statement on ethical criteria for human research in Canada, the Tri-Council Policy Statement (Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada), recognizes the potential for conflict of interest with commercial REBs, but the document does not discuss commercial REBs any further (25). As of a few years ago, Health Canada did not even know how many such agencies were operating in the country (24).

Problems with REBs are not just confined to the for-profit sector. Academic-based REBs were described in the Law Commission report as “overburdened [and] . . . stretched to the breaking point. . . . As the work becomes increasingly complicated with globalization, technology and commercialization, REBs are struggling to find committee chairs or even members. . . . REB members have barely begun to grapple with the ways in which cultural differences may demand different approaches, particularly to informed consent” (22).
These difficulties may help to explain serious breaches in the behavior of academic REBs documented in a series of anecdotal reports. The University of British Columbia failed to warn patients of all the dangers and side effects of study medications for years (26). The REB at the St. Joseph’s Healthcare Centre in Hamilton approved a study that involved distributing a questionnaire to Catholic high school girls about problems with menstruation. However, the survey consent form did not include the fact that the questionnaire was being used as a screening form to find girls who would then be asked to join a trial studying the use of Prozac for severe premenstrual syndrome (27). U.S. investigators found that the McMaster University REB had been failing to properly review experimental pediatric cancer protocols and that consent forms “given to guardians of the children were incomplete, hard to understand, and tended to minimize the potential risks while overstating the potential benefits” (28).

RECRUITING DOCTORS AND PATIENTS FOR TRIALS

Estimates of the number of Canadians taking part annually in clinical trials range from 100,000 to 1.8 million (29). In order to get them to identify and enter patients into these trials physicians are paid anywhere from a few hundred dollars a patient to $6,000 per patient in the case of a trial sponsored by Merck Frosst (30). In some cases physicians and academics who are engaged in multiple trials for drug companies can earn as much as $500,000 per year from this activity (29). Although doctors and the agents who recruit them may claim that money is not an issue and that they are participating in the research to keep on the cutting edge of therapeutics and for the benefit of their patients (31), that is not the view of Dr. Paul Flynne, assistant registrar of the College of Physicians and Surgeons of Alberta (32).

Inclusion in and exclusion from clinical trials is important because when a drug initially appears on the market, information gained in clinical trials is all that is available to doctors and patients to judge how well a product works and what its side effects may be. If certain groups are not included in clinical trials, when doctors prescribe for these groups they have little or no information to guide them.

After the thalidomide disaster in the early 1960s, women of child-bearing age were generally systematically excluded from clinical trials. This situation did not formally change in Canada until 1997 when Allan Rock, then minister of health, announced a guideline on the inclusion of women in clinical trials. However, this guideline only encouraged the inclusion of women, it did not make their inclusion mandatory and the guideline cannot be enforced (33). Despite the guideline, in the late 1990s HIV-positive women still seemed to be underrepresented in clinical research (34). In 1999 the Women’s Health Strategy of Health Canada promised to monitor compliance with the guideline on the inclusion of women in clinical trials, but as of early 2003 no systematic mechanism was in place to do so (35).
There is also only a nonenforceable guideline on the inclusion of children in clinical trials (36). While Health Canada says that it “reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product,” whether or not it has exercised its prerogative to demand additional conditions regarding the inclusion of children is impossible to determine.

THE CONDUCT OF CLINICAL RESEARCH

There are anecdotal cases that demonstrate either a lack of monitoring by Health Canada or a lack of concern about regulations being violated. Officials in Health Canada have admitted that some trials were allowed to proceed before being approved by the organization, because they had been reviewed by U.S. authorities (37). Only after a man with tuberculosis was included in a Phase I trial (a trial in healthy people) in Montreal in 2005, potentially exposing all of the other trial participants as well as the people running the trial to infection, did Health Canada create guidelines that required screening of trial participants for symptoms of the disease (38, 39). Although the person in this case was apparently showing signs of the disease, SFBC Anapharm, the company running the trial, was able to keep him in the on-site study.

Before 2002 Health Canada did not monitor the conduct of clinical trials. New regulations to allow for inspections were introduced as part of the package that reduced the time for reviewing Phase I trials from 60 to 30 days. In 2003–2004 a total of 45 trials were inspected—23 run by commercial sponsors and 22 by noncommercial sponsors, or about 2 percent of all the trials in the country (40). Health Canada says that it uses “risk-based criteria” to select the trials to be inspected, but these criteria—the number of subjects enrolled and the number of trials conducted at a specific location—are vague. It is unknown whether Health Canada is actually monitoring the trials in which the participants are at the greatest risk. Program managers at Health Canada consider there is an insufficient level of activity at Health Canada on investigating clinical trials (15).

The degree to which Phase IV trials—those done after a drug has been approved and is being marketed—are monitored is a significant cause for concern. This type of trial is typically run in a community setting and has therefore been approved by a for-profit REB. Moreover, Phase IV trials are often used by industry not to generate new scientific data but to generate interest about the drug among the doctors involved in the trials and get them familiar with prescribing the product (41). Health Canada’s new inspection process can be applied to these trials

---

“as needed” (40), but what that means is not spelled out and the 2003–2004 report does not detail whether any trials of this type were inspected.

Although commercial interests have always played a significant role in clinical trials, commercial considerations are becoming an increasingly important factor in the decision about when to terminate clinical research. One manifestation of the trend to commercialize research is that pharmaceutical companies are turning over their management to companies known as Contract Research Organizations (CROs), largely a phenomenon of the past two decades. Echoing a common theme about many aspects of clinical trials, “observers worry there is very little oversight or information about private CROs” (2).

The common explanation for the rise in prominence of CROs is that they can run trials more efficiently than pharmaceutical companies and therefore save money. Mirowski and Van Horn (42) see the CRO as representing much more, as yet another manifestation of the privatization and commercialization of scientific research. CROs are private companies hired by pharmaceutical firms and, unlike academic researchers, they have no inherent interest in the data they are collecting and are therefore much more willing to keep the results secret rather than seeking to publish them. CRO employees who do the research are not oriented to publication nor do their careers depend on the number of journal papers they produce. CROs are also linked to the rise in ghost authorship, whereby pharmaceutical companies pay medical writers to write up studies and then look for researchers willing to sign their names to the studies.

**HOW ARE TRIALS ANALYZED AND WHAT DOES HEALTH CANADA DO WITH THE DATA?**

As mentioned earlier, results from clinical trials provide nearly all of the early information about how to use new drugs properly. Even if drug trials include members from various groups of the population, the analysis of the trials will not necessarily take into account the differences among groups—for example, results for elderly participants may not be analyzed separately from the general results. Lippman points out that although the guideline about women in clinical trials suggested that “patients of both sexes . . . [should] be included . . . in numbers adequate to allow detection of clinically significant sex-related differences in drug response” (33), there was nothing in the guideline to make this a mandatory requirement. Further, she argues that “there is still more adjustment for, than analysis by, sex in reported research” (33). In support of her position, in the mid-1990s, of 43 trials on therapy for acute heart attacks only 14 provided gender-related results (43).

One crucial factor in how clinical trials are analyzed is the relationship between the investigators and the organizations paying for the research. The latter are usually for-profit companies, primarily from the pharmaceutical industry. At present, there is little systematic knowledge about the interactions between clinical
researchers and commercial organizations in Canada. A recent survey of 107 medical schools in the United States found that in some areas the medical schools allowed considerable lenience. Whereas nearly all of the schools prohibited the sponsor from making the decision about whether the results should be published and did not give the sponsor the right to make revisions to the manuscript written by the investigator, 50 percent allowed the sponsor to draft the manuscript and 80 percent permitted the sponsor to own the data (44).

The University of Toronto recently revised its research agreement with its affiliated teaching hospitals. Among the principles adopted to guide negotiation of research contracts were ones prohibiting research sponsors from suppressing or otherwise censoring research results and stipulating that investigators be allowed to submit work for publication within 6 months of sharing the findings with the sponsor. A review of 152 clinical study agreements signed in a 6-month period, conducted shortly after the agreement was reached, found that 100 percent of the agreements did not allow any censorship or suppression and more than 90 percent complied with a maximum publication delay of 6 months (45). Further follow-up has either not been done or is not publicly available.

When drug companies seek approval for new drugs they must file information on all trials that have been conducted on the drug, whether done in Canada or in other countries. In addition, all safety information must be submitted. What Health Canada does with these data is largely a mystery to people outside the department and the drug company, as this information is regarded as commercially confidential and will not be released by Health Canada without the permission of the company. Even the reviews by Health Canada are not public documents, because they refer to data regarded as the company’s private property. Non-disclosure of the information in clinical trials has serious disadvantages for Health Canada, health professionals, and the Canadian public. If scientific data submitted to regulatory agencies are never disclosed or allowed to enter normal peer-review channels, neither these data nor the reviewers’ evaluations can be subject to scrutiny by independent scientists. The scientific atmosphere of the agency may be stifled and the professional growth of its staff severely inhibited. Deprived of any independent access to information, health professionals and the public must accept Health Canada’s judgment about the safety and effectiveness of products (46).

In response to calls for greater transparency, Health Canada announced in 2004 that when new drugs and devices were approved it would publish a document entitled a Summary Basis of Decision (SBD). The SBD would outline the scientific and benefit-risk-based reasons for the decision to grant market authorization for the product (47). The key part of the SBD of importance to prescribers and consumers is the clinical information on drug effectiveness and safety. Is enough information provided to allow for the safe and rational use of new medications or for the extension of indications for previously approved drugs? In at least three cases where access to information held by regulatory
authorities revealed either misrepresentation of clinical data or significant safety issues the answer is no, the amount of information in the SBD would not have been sufficient to uncover these problems (46).

CLINICAL TRIAL REGISTRIES

In recent years, a couple of high-profile scandals have led to a growing call for transparency in the results of clinical research. First, GlaxoSmithKline did not publish results showing 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” (48). Second, 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” (49). One result of both revelations was the strengthening of the demand that all clinical trials be registered in on-line, publicly accessible databases that contain key information about clinical trials. Although major companies such as Merck support the idea of a clinical trial registry (50), actual compliance by industry in accurately entering data into existing registries leaves room for substantial improvement (51).

Health Canada has begun discussions about registering clinical trials conducted in Canada. A workshop on this topic was held in June 2005, an external working group met in April 2006, and in June and July 2006 people were given the opportunity to complete an on-line questionnaire on the topic (52). The external working group delivered its report in December 2006 (53). 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” (54). No time line or process is given for making the final decision.

CONCLUSION

Without clinical trials drug development would grind to a halt and we would be left with a situation in which anecdotal data were all we had to rely on for judging how safe and effective drugs are. No one wants this situation, but the current state of affairs with respect to clinical trials is not acceptable. The major themes that have emerged from this analysis are the influence of the profit motive in all aspects of clinical trials and the unwillingness of Health Canada to forcefully assert the public interest. This tilt by Health Canada in favor of industry echoes what has been seen in the drug approval arena. As industry contributed an increasing share of the budget for drug regulation, drug approval times dropped and the approval rate of applications for marketing increased (55).
At the extreme, there are two competing visions of what the prime function of a drug regulatory authority should be. The position put forward by the pharmaceutical industry holds that the main function is to facilitate industry’s efforts to develop new products and to approve them as quickly as possible. In this view, medications are commodities and the regulatory authority exists to provide a service to the industry. The second view, espoused by consumer groups and public health activists, sees the primary purpose as appropriately evaluating products to ensure a high standard of effectiveness and safety. Here, medications are seen as an essential element of the health care system and the regulatory authority exists to provide a service to the public.

The shift in drug approvals and the subjugation of public interests to those of the industry in the clinical trials arena raise serious concerns, based on principal-agent and capture theories, about whether Health Canada’s primary commitment is still to public health. 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 perform the task in exchange for compensation. Before the introduction of user fees and the push to develop the clinical trials industry in Canada, the principal was the public and the agent was the relevant regulatory authority. However, now a new principal has been added: the pharmaceutical industry that is providing a substantial fraction of the money needed to run the drug regulatory system and that funds clinical trials. Regulatory capture theory asserts that over time regulators tend to become advocates for the industry they are supposed to regulate, as a result of conflict avoidance and influence from the industry. The theory predicts that over time, regulatory authorities will become less receptive to the needs of the public and will more closely align their missions with that of the pharmaceutical industry (56).

The apparent reorientation of Health Canada in favor of business interests is further reflected in the Business Transformation Strategy that is being implemented for the Therapeutic Products Directorate. The strategy was introduced in early 2003 and “builds on the commitments made by the Government of Canada to ‘speed up the regulatory process for drug approvals,’ to move forward with a smart regulations strategy to 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” (57).

One of the key phrases in the Business Transformation Strategy is “smart regulation,” which means that Canada should “regulate in a way that enhances the climate for investment and trust in the markets” (58). While health is not ignored, the emphasis is clearly on creating a business-friendly environment (59). The federal External Advisory Committee on Smart Regulation explicitly states that risk management has an essential role in building public trust and business confidence in the Canadian market and regulatory system (60). Once again, the business agenda takes a prominent position. The willingness to give
CROs seemingly unfettered access to run clinical trials as they see fit is a reflection of the move to smart regulation.

When applied to clinical trials, risk management would mean weighing potential negative effects against potential advantages. Potential negative effects would be adverse health effects that could occur under reasonably foreseeable conditions (61). The shift from the precautionary principle to risk management is subtle but unmistakable. According to the precautionary principle, if products cannot be shown to be safe then they should not be marketed; risk management allows products on the market unless they are shown to be harmful. Realigning regulation to conform to the principles of smart regulation would not totally abandon the concept of precaution, but seems to imply that there would have to be a threat of serious or irreversible damage before it would come into play. An example of the triumph of risk management over the precautionary principle is what happened with the trial run by SFBC in Montreal, described above. Only after someone in the trial was showing signs of tuberculosis did Health Canada move to impose health restrictions on who could participate in these trials.

Despite Health Canada’s professed desire for more openness and transparency, it continues to deny public access to basic efficacy and safety information derived from clinical trials and is moving at a snail’s pace in developing a policy on clinical trials registration. Once again, these policies demonstrate a prioritization of industry’s needs over those of the public.

If clinical trials are to serve the purpose for which they are designed—developing reliable and objective information about new drugs—then commercial interests as represented in concepts such as smart regulation and risk management need to be explicitly rejected in favor of health interests.

REFERENCES


32. Munro, M. Drug firms pay $3,000 or more per patient for trials. *Vancouver Sun*, February 24, 2004.


Direct reprints requests to:

Dr. Joel Lexchin
School of Health Policy and Management
York University
4700 Keele Street
Toronto, ON M3J 1P3
Canada

e-mail: jlexchin@yorku.ca