

## Clinical trials regulation — how Canada compares

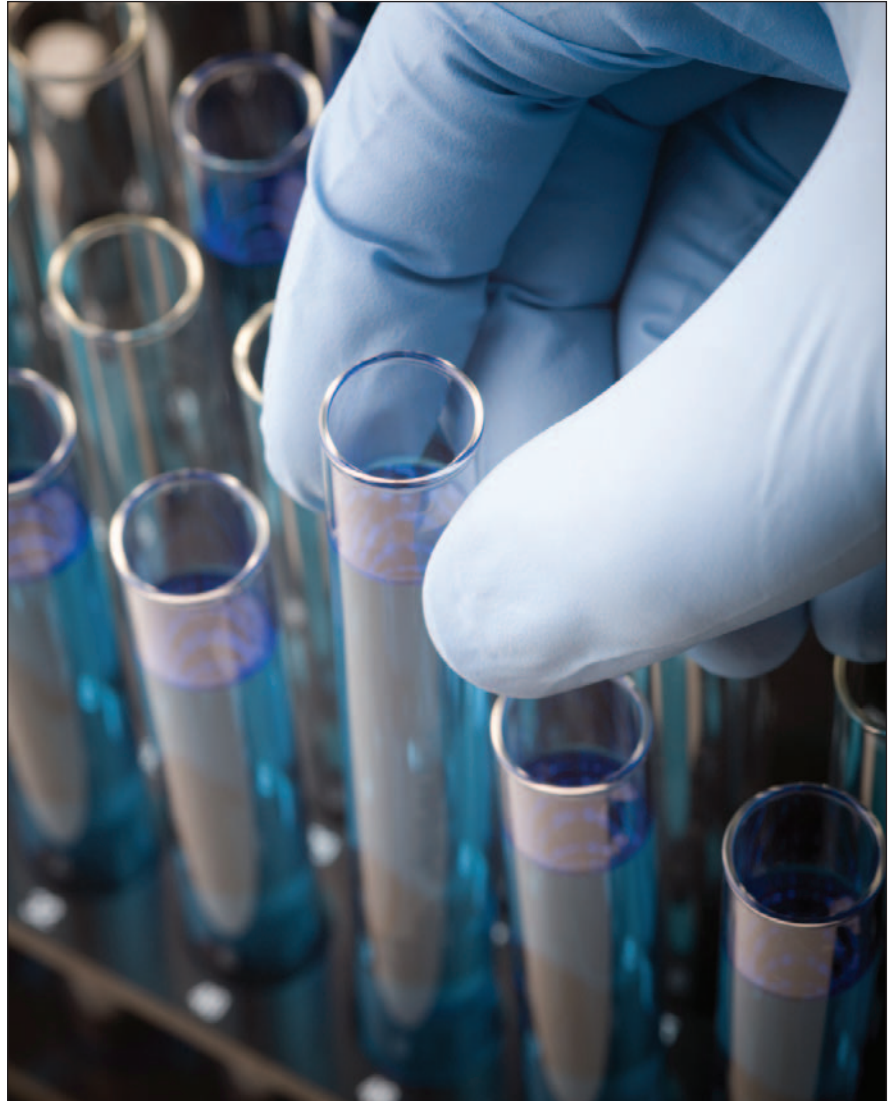
When a 48-year-old man with no history of cardiac problems suffers 2 heart attacks and dies during a testing of a new drug, it is axiomatic that concerns will resurface about the safety of clinical trials.

To clear his debts, Peter Munro, a healthy and athletic father of 3, had volunteered for a phase 1 trial of RhuDex, a new drug being developed by the German pharmaceutical company MediGene to treat rheumatoid arthritis. If the resident of Edinburgh, Scotland, had completed the trial, he would have been paid £2000 (about \$4019). Instead, the bodybuilder is 6 feet under, his death is under investigation by the United Kingdom's Medicine and Healthcare Products Regulatory Agency, and his family is seeking legal redress and the closure of the Charles River Clinic in Tranent, near Edinburgh.

His death raised the spectre of the infamous phase 1 drug trial that 2 years earlier had sent 6 healthy men into survival watch in intensive care due to multiple organ failure that occurred during the testing of the immunomodulatory drug candidate TGN 1412, which was being developed by the now-bankrupt German biotech firm TeGenero and was being tested at London's Northwick Park Hospital. A 24-year-old was left without toes, while a 26-year-old man was dubbed "The Elephant Man" after his head swelled to nearly double its original size.

The reaction was swift. An ensuing inquiry revealed gaps in the UK's system for overseeing clinical trials and by 2007, the frequency of trial inspections was significantly increased.

It also put the international spotlight back on clinical trial regulation and inspection. Hard worldwide numbers about clinical trial participation are all but nonexistent, although it's estimated about 3.5 million Americans are enrolled annually. Canadian cancer groups have estimated that 7000–10 000 Canadians are enrolled in cancer trials, but neither Health Canada



Photos.com

Health Canada has been reviewing its clinical trials regulatory processes for the better part of 2 years but, as yet, nothing in the way of proposals for restructuring or improving the system has surfaced.

nor the Canadian Institutes of Health Research have data on participants, many of whom are recruited by family physicians.

As a result of clinical trials mishaps, the UK and United States have been moving quickly to reform their oversight regimes. Canada, by contrast, has not sought change with any measure of alacrity. Health Canada has been reviewing its clinical trials regulatory

framework for nigh on 2 years and has conducted stakeholder consultations. But nothing in the way of a report or new proposals for restructuring the system have yet surfaced.

In general, regulators in Canada, the US and the UK use inspections as their principal means of oversight of clinical trials but recent history demonstrates that the approach has limitations, largely because of resource constraints.

In the US, for example, Inspector General Daniel Levinson reported in September 2007 that the US Food and Drug Administration (FDA) had little clue about the number of clinical trials being conducted, audited fewer than 1% of those and typically inspected after the tests were completed. With a scant 200 inspectors overseeing an estimated 350 000 sites, they almost never fol-

lowed up inspections to determine if corrective action was taken and in 68% of all inspections, downgraded their findings. Levinson concluded that the FDA lacked the necessary “comprehensive management and reporting systems,” to meet objectives.

Meanwhile, the TGN 1412 debacle, which ultimately led to revisions in British guidelines for clinical trials and

tightening of regulations surrounding phase 1 studies, “certainly woke people up to the fact that the system was not working,” says Dr. Michael Goodyear, an oncologist at Dalhousie University in Halifax, Nova Scotia.

Although Canada has thus far been spared such disasters, events in the UK should raise alarms here, Goodyear adds. “It could have happened here just

## Canada lags the United States in transparency of clinical trial information

Critics cast Health Canada’s clinical trials oversight programming as a black hole from which information never emerges. The lack of disclosure and transparency was nowhere more evident than in a 2006 case involving a man who enrolled in Montréal, Que.-based trial despite having active tuberculosis. When Health Canada investigated, it learned that 9 healthy trial participants subsequently had a latent tuberculosis infection, as did more than 10 employees of Anapharm, the company managing the trial.

But Health Canada never released a report about its investigation or the problems it discovered. It took a Canadian Press freedom of information request for internal Health Canada documents for any details to become known.

If nothing else, the Montréal episode highlights “that the procedures in Canada are much more secretive than in the US,” says Trudo Lemmens, professor of law and bioethics at the University of Toronto.

For its part, Health Canada says privacy and confidentiality rules preclude it from disclosing any details when it suspends a clinical trial, including information such as the name of the investigator or the type of trial.

But critics say Canadian agencies use the privacy laws as a smokescreen and fail to reveal information that should be readily accessible to the public. “Canada is a black box,” with regard to health research, says Dr. Charles Weijer, Canada Research Chair in Bioethics at the University of Western Ontario in London, Ont.

Yet, Health Canada officials take pride in their privacy protections. “Subject protection matters in Canada are rapidly evolving,” departmental spokesperson Agnes Klein says, adding that “they are rapidly becoming in many ways somewhat stronger than in other jurisdictions because of the nature of the regulations under which we operate.”

On the issues of privacy and confidentiality, Canadian regulations are among “the strongest, tightest and most restrictive” in the Western world, Klein says.

But in practice, it’s not clear that the restrictions are applied to protect human subjects. For example, Health Canada worked with the Canadian Institutes for Health Research (CIHR) to develop its ethics guidelines. But Weijer says that when he recently asked CIHR about its

research integrity committee, he was told privacy law precluded disclosure of the names of nongovernmental employees on the committee.

In Weijer’s view, that’s misrepresenting the privacy laws in order to protect government secrets. “At least with respect to CIHR, the misrepresentation is transparent,” he says. While Health Canada did, at the end of 2004, publish a one-year summary of inspections, no further reports have since been published. (In fact, Health Canada has no obligation to report on its inspections of clinical trials.)

In contrast, the results of US Food and Drug Administration inspections are listed on the agency’s website ([www.fda.gov](http://www.fda.gov)). When an inspection finds serious problems, its warning letter — known as a “Notice of Initiation of Disqualification Proceeding and Opportunity to Explain” — is also posted, albeit with some delay and certain information blacked out.

The FDA also publicly posts its notorious blacklist: a list of clinical researchers found guilty of misconduct.

Back in Canada, there is virtually no information available from Health Canada regarding its inspections, even in cases where the FDA has reprimanded a Canadian researcher. In 2003, the FDA investigated a pediatric clinical trial taking place at the Children’s Hospital of Eastern Ontario in Ottawa, Ont. and issued a warning letter about violations to Dr. Jacqueline Halton, who was involved in running the trial. The letter, posted on FDA’s website, told Halton that if she failed to effectively implement corrective actions or committed other violations, “enforcement actions” could follow. Health Canada subsequently investigated the trial but released no information about the doctors or 7 other trial centres involved. It was later revealed that a 4-year-old boy died after being given an overdose of the cancer drug Interleukin-2, at a time when the trial had not yet received Health Canada approval to proceed. Months later, that authorization was obtained and the trial continued. Health Canada has never publicly reported on the case.

Unlike the US, where the Inspector General of the Department of Health & Human Services scrutinized FDA processes and practices, there has also been no independent assessment of Health Canada’s clinical trials inspectorate.

as easily. There was nothing specifically about the UK that was lax.”

Moreover, there’s an increased likelihood, given the growth of clinical trials in the country. And given that Health Canada doesn’t maintain a clinical trial registry, data about the number of trials is somewhat imprecise.

Health Canada reports show that the total number of phase 1 clinical trial applications rose to 1118 from 714 in Canada between 2002 and 2007, while the overall total (including phase 2 and 3 trials, the number of which have been in a steady-state or a decline) rose to 1724 in 2007 from 1287 in 2002.

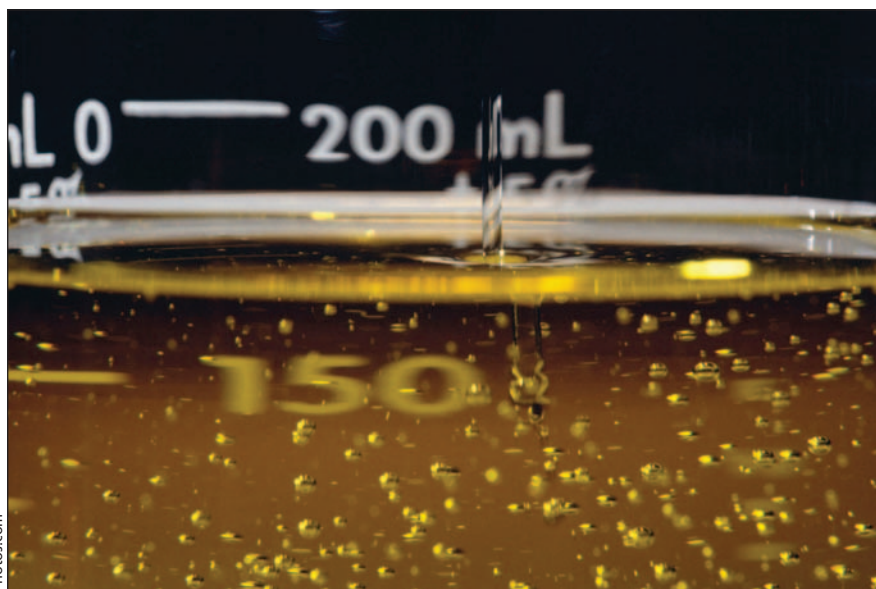
In short, almost all of the clinical trials growth has been at the phase 1 level, reaffirming the widely held notion that phase 1 trial units are sprouting up like mushrooms across the nation. This is largely due to changes in 2001 that shortened the standard Health Canada review for phase I trials in healthy volunteers to 7 from 60 days. The government widely advertised its new, shorter approval times, along with its low tax rates for companies involved in research and development, in a bid to attract companies sponsoring clinical trials. Health Canada officials even got the word out by attending meetings and writing articles.

The upshot has been that CenterWatch, a private firm in Boston, Massachusetts which gathers data on the industry, says Canada now ranks second in the world in terms of its number of clinical trial sites, following the US, but ahead of Germany, France and the UK.

Oversight, though, is hardly following the same growth curve.

Over the past few years, Health Canada has ramped up its inspection activities “at least to the equivalent of the FDA’s,” says spokesperson Agnes Klein, director of the department’s Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics. That may well be true, although the limited data available suggests that the level of inspection still falls well below a target of 2% of trials.

In fact, in fiscal year 2006/07, according to a Health Canada presentation at the 4th annual Clinical Trials in Canada conference in April 2008, the department’s 39 “Qualified Investigators” managed to inspect 40 trial sites,



Canada now inspects a scant 1% of clinical trials, or less than half of Health Canada’s stated goal of 2%. Meanwhile, Canada now ranks second in the world in terms of the number of clinical trial sites it hosts.

or about 1% of sites with ongoing trials. (The number of inspected Canadian sites is actually somewhat higher as the figure doesn’t include Health Canada investigations in response to a complaint; FDA inspections of FDA approved trials in Canada and US National Institutes of Health inspections of trials they fund here. According to CenterWatch, 128 international inspections took place in Canada between 1980 and 2006. About 60% of FDA inspections in Canada between 2002 and 2006 resulted in a requirement for voluntary action by the sponsor).

Although similar to the level achieved in the US, Health Canada spokesperson Paul Spendlove says the inspectorate’s objective is to conduct approximately 80 inspections per year.

The UK’s 60 inspectors managed inspections of 96 trial sites in 2006, about one quarter of which resulted in a critical finding. If a response to such a finding is inadequate, it can lead to a re-inspection or referral to the agency’s inspection action group but press officer Jennifer Kyne says the agency has only very rarely exercised its authority to stop a trial.

Canadian regulators have proved no more eager to intervene.

Health Canada has been known to stop trials in midstream twice since

2001, when new clinical trial regulations were adopted. Prior to that, trial oversight was primarily the purview of the local research ethics board that had approved the protocol.

Klein says that in the most recent case in which her office stopped a trial, “we discovered a couple of instances of potentially unwarranted risk taking in 1 instance with 1 investigator, and we actually have requested that he suspend studies until he satisfies us with what he does and how he does things.” Departmental spokesperson Stéphane Shank says privacy and confidentiality issues preclude disclosure of further information about the trial.

Another known suspension involved a drug being tested in Germany and Canada. Dr. Siddika Mithani, then-head of Health Canada’s clinical trials program, halted that trial after learning of the death of a healthy volunteer in a parallel German trial. During a talk at Dalhousie University in 2003, Mithani, who now directs Health Canada’s veterinary drugs directorate, said that she informed the sponsoring firm “not on my watch. You’re not doing that trial in Canada.”

Dr. Robert Peterson, who was head of Health Canada’s therapeutics products directorate at the time, says he knew of several similar situations involving trials in Canada that were stopped when spon-

sors were reprimanded by another country. “If the regulator in the other country said, ‘Wait a minute, we’ve got a problem; we’re going to suspend your licence’, I can tell you that would terminate a clinical trial here pretty quickly.”

According to Health Canada’s Paul Spendlove, the department “has not changed its processes in any way,” since the period referred to by Mithani and Peterson. But the department issued only one “Not Satisfactory” letter to clinical trial applicants between 2004 and 2007, as compared with 5 in 1999, 2 in 2000, 7 in 2001, 4 in 2002 and 4 in 2003.

Klein says Health Canada’s inspection processes “parallel” those of the UK and US but the Canadian inspectorate is smaller than its counterparts; its inspections are fewer and it severely lags in issuing reports (sidebar, page 636). Dr. Stuart Macleod, a drug safety expert at the University of British Co-

Canada also lags in any form of oversight of trials conducted outside its borders on products whose manufacturers are expected to seek regulatory approval from Health Canada. Departmental spokesperson Alistair Sinclair stated in an e-mail that for trials with sites in “India, China or other countries,” the department relies on “international guidelines for the conduct of clinical trials” and monitoring by “sponsors and other regulatory agencies.”

The migration of clinical trials to Eastern Europe, Latin America, India and China has been inexorable in recent years as the pharmaceutical and biotechnology industry move to take advantage of lower costs, larger populations of potential research subjects and less restrictive regulations. But it’s come at the cost of spate of drug trial horror stories, prompting the World Medical Association to move to

one of those brochures, “are regularly monitored by Health Canada, the US FDA and industry sponsors.” — Dr. Miriam Shuchman, Toronto, Ont.

DOI:10.1503/cmaj.081271

## Moratorium urged for foreign visa trainees

**A**t a time when Canada has a shortage of doctors, and qualified Canadian and international medical graduates are waiting in the wings to be certified, concerns are being raised about the number of foreign visa trainees in Canadian residency programs.

The Association of International Physicians and Surgeons of Ontario President Dr. Joshua Thambiraj, for example, estimates that only 20% of qualified international medical graduates in the province are getting residencies each year.

Meanwhile, Canada is providing residency spots and “training hundreds of foreign visa trainees who go back to their own countries, so they’re not able to solve the doctor shortage in the province, or contribute in any way to Canada.”

Thambiraj says that a logical solution to the backlog of international medical graduates waiting for residencies would be to place a moratorium on foreign visa trainees for 2 or 3 years.

Foreign visa trainees can be students in Canadian medical schools, residents, or postgraduate fellows. Many of them come from the Middle East, but they also come from Europe and the United States. Their governments typically pay their tuition and living expenses on the proviso that they return home to practise.

The Canadian Resident Matching Service pairs Canadian-trained medical school graduates with residency positions. No more than 1 or 2 visa trainees from any Canadian medical school can enter the match, which is generally restricted to Canadian citizens and permanent residents, says Danielle Cameron, an agent for the service. Sponsoring governments make arrangements directly with faculties of medicine.

“It could have happened here just as easily. There was nothing specifically about the UK that was lax.” — Dalhousie University oncologist Dr. Michael Goodyear

lumbia, is concerned that Health Canada doesn’t have sufficient personnel “to do what they’re trying to do.”

Peterson, who left Health Canada in 2005, says the trials inspectorate was “resourced adequately” at that time but he worries that staff levels have not since kept pace with need.

The department also lacks what many would call basic data. Although it is working on a process for registration of clinical trials, this effort has lagged and there is now no trial registry, or even a registry of research ethics boards in Canada.

The latter is a real shame, says Goodyear, former chair of Dalhousie’s research ethics board. “We have no way of finding out how many REBs there are in Canada and who they are and where they are,” he says, adding that the problem is particularly acute in British Columbia, Quebec and Ontario, where private ethics boards often oversee clinical trials.

update its cornerstone guidelines on ethical trial conduct (*CMAJ* 2008;178 [2]:138).

The FDA, meanwhile, has moved to expand its capacity to conduct inspections in the developing world, promising to establish satellite offices in China, India and South America (*CMAJ* 2008;179[2]:131). Inspectors based overseas will mostly oversee manufacturing facilities, but they may also be in a position to monitor clinical trials.

For its part, the federal government seems focused on promoting Canada as a trials site and stemming the flow of trials to the developing world. At the Biotechnology Industry Organization’s international meeting in San Diego in June, Industry Canada distributed literature promoting the nation as a competitive candidate for commercial clinical trials due to its low institutional overhead costs, thriving contract research industry and streamlined regulatory process. “Canadian trial sites,” states