NEWS

Canada makes clinical trial data available to public

BY **UNDARK**

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This past March, Canada’s health department changed the way it handles the huge amount of data that companies submit when seeking approval for a new drug, biological treatment or medical device -- or a new use for an existing one. For the first time, Health Canada is making large chunks

of this information **publicly available** after it approves or rejects applications.

Within 120 days of a decision, Health Canada will post clinical study reports on a new government online **portal**, starting with drugs that contain novel active ingredients and adding devices and other drugs over a four-year **phase-in period.** These company-generated documents, often

running more than 1,000 pages, summarize the methods, goals and results of clinical trials, which test the safety and efficacy of promising medical interventions. The reports play an important role in helping regulators make their decisions, along with other information, such as raw data about individual participants in clinical trials.

So far, Health Canada has posted reports for four newly approved drugs -- one to treat plaque psoriasis in adults, two to treat two different types of skin cancer, and the fourth for advanced hormone-related breast cancer -- and is preparing to release **reports** for another 13 drugs and three medical devices approved or rejected since March.

Canada's move follows a similar policy enacted four years ago by the European Medicines Agency (EMA) of the European Union. The U.S. Food and Drug Administration (FDA), on the other hand, continues to treat this information as confidential to companies and rarely makes it public.

Transparency advocates say clinical study reports need to be made public in order to understand how regulators make decisions and to independently assess the safety and efficacy of a drug or device. They also say the reports provide medical societies with more thorough data to establish guidelines for a treatment's use, and to determine whether articles about clinical trials published in medical journals -- a key source of information for clinicians and medical societies -- are accurate.

"Sometimes regulators miss things that have been hidden in those clinical study reports," says Matthew Herder, director of the Health Law Institute at Dalhousie University in Nova Scotia. "Regulators often face resource constraints, they have deadlines, other priorities."

Last year, for example, researchers in Canada used a clinical study report and other previously non-public information from a clinical trial to **call into question** the efficacy of Diclectin (known as Diclegis in the United States), a commonly prescribed drug to treat nausea and vomiting in pregnancy. The team had requested the information from Health Canada under an older policy, which required researchers to sign a confidentiality agreement and keep the underlying data secret when they published their results. (It "had a chilling effect," Herder says of the now-discontinued policy, and not many researchers made requests.)

Duchesnay, the Quebec-based manufacturer of Diclectin, **defended** the drug, and the Canadian and American professional societies of obstetricians and gynecologists continue to recommend it. Yet the new analysis gave pause to the College of Family Physicians of Canada, which had previously published two articles recommending Diclectin's use in its medical journal, *Canadian Family Physician.* The organization took the unusual step in January of publishing a **correction**, which criticized the independence and accuracy of the two earlier articles. And, citing the new research, it advised physicians to use caution when interpreting recommendations for the drug's use.

Urging transparency:

Herder and other lawyers and independent researchers who want to see greater transparency in medical research are urging the FDA to follow the example of Canada and the EU, but without success thus far. To date, the European **program**, which has been in effect since 2016, has posted clinical study reports for 132 medicinal products whose applications were submitted after January 2015.

It is important to have multiple regulators making the data public, says **Peter Doshi**, associate editor at *The BMJ*, an international medical journal, and associate professor of pharmaceutical health services research at the University of Maryland School of Pharmacy. As it stands now, “if FDA approves first, which often it does, we won’t know anything until Health Canada or the EMA makes a decision,” Doshi says. “And not every drug, device, biologic out there is going to be approved by these other regulators or even submitted to these other markets.”

In addition, redundancy lessens the impact if one regulator changes policy. The EMA, for example, earlier this year moved its operations from London to Amsterdam because of Britain’s anticipated exit from the European Union. Clinical data publication “was one of the activities suspended until we are more settled in Amsterdam,” says Anne-Sophie Henry-Eude, head of documents access and clinical data publication. No date has yet been announced for its resumption.

Sandy Walsh, a spokesperson for the FDA, says the agency does not have the same freedom as Canadian and European regulators to release clinical study reports. “U.S. laws on disclosure of trade secret, confidential commercial information and personal privacy information differ from those governing EMA and Health Canada’s disclosure of clinical study reports,” she wrote in an email.

Some legal experts argue the FDA has more flexibility than it acknowledges. Federal agencies are “entitled to substantial deference" in determining “what constitutes confidential commercial information,” **Amy Kapczynski**, professor of law at Yale University and co-director of the university’s Collaboration for Research Integrity and Transparency (CRIT), and **Jeanie Kim**, then a Yale Law School research scholar, wrote in a **2017 article** in the *Journal of Law, Medicine & Ethics.*

In response to an interview request sent to the Pharmaceutical Research and Manufacturers of America (PhRMA), Megan Van Etten, the trade group’s senior director for public affairs, emailed a statement expressing concern from the industry that Health Canada’s new regulations “could discourage investment in biomedical research by revealing confidential commercial information.”

Joseph Ross, associate professor of medicine and public health at Yale University and a co-director, along with Kapczynski and others, of CRIT, maintains that clinical study reports contain little information that companies need to keep secret, and that any such information could be redacted before release. A **2015 report** by the Institute of Medicine, now known as the National Academy of Medicine, also called for the FDA to release redacted clinical study reports.

That is the strategy of Health Canada, which discusses possible redactions with the manufacturer. “Health Canada retains the final decision on what information is redacted and published,” Geoffroy Legault-Thivierge, a spokesperson, wrote in an email.

So does the EMA, which goes through a similar negotiating process with manufacturers. “We often are in disagreement, but at least there is a dialogue,” says Henry-Eude. The EMA might agree to redact manufacturing details, for example.

Revealing bias:

Researchers who independently re-evaluate drugs say the reports are critical because the data they need is not readily available in medical journal articles. **One analysis** showed that only about half of clinical trials examined were written up in journals in a timely fashion, and a third went unpublished. And when articles are published, they contain much less data than the reports, says Tom Jefferson, an epidemiologist based in Rome who works with Cochrane, an international collaboration of researchers who conduct and publish reviews of the scientific evidence for medical treatments.

In addition, “journal articles emphasize benefits and underplay or, in some cases, even ignore harms” that can be found in the clinical study report data, Jefferson says. **An analysis** by experts at the Institute for Quality and Efficiency in Health Care in Cologne, Germany, found “considerable” bias in how participant outcomes were reported in journal articles and other publicly available sources. Public access to clinical study reports can shine a light on such discrepancies.

The FDA has flirted in the past with releasing clinical study reports to the public. In January 2018, it launched a **pilot program** to post portions of reports for up to nine recently approved drugs if the drug companies would agree.

“We’re committed to enhancing transparency about the work we do at the FDA,” commissioner **Scott Gottlieb**, who resigned in March, said at the time.

But only Janssen Biotech, a subsidiary of Johnson & Johnson, volunteered, and its prostate cancer drug Erleada is the **lone entry**. In June, the FDA **announced** it is considering shifting its focus from the pilot program to another designed to better communicate the analyses of FDA experts who review drug applications, which the agency has been making public for approved medicinal products since 2012.

But these analyses by FDA reviewers are no substitute for the actual clinical study reports, Doshi says. The reviews reflect “an FDA scientist’s take on the sponsor’s application,” he says. “Without the clinical study report, somebody like me is largely deprived of looking at the underlying data and developing my own take.”

Independent researchers like those who took a hard look at Diclectin also want access to clinical study reports connected to regulatory decisions made before the European and Canadian portals were opened.

Since 2010, the EMA has been providing researchers and others with access to clinical study reports for such legacy drugs upon request, whereas Health Canada is even more transparent, posting requested clinical study reports for drugs and devices approved or rejected before March to its new online portal for anyone to see. So far, 12 information packages **are available** for older drugs and devices, and 11 more requests **are being processed**.

'Big black boxes':

The FDA has, on occasion, provided reports in response to a Freedom of Information Act (FOIA) request, but researchers seeking this information typically invest “a tremendous amount of time and effort,” Ross says. For example, a Yale Law School clinic sued the FDA on behalf of two public health advocacy groups after the agency said it could take years to respond to their FOIA request for clinical trial data for two hepatitis C drugs. In 2017, it won the case and the groups received the data, which they are currently evaluating.

The FDA does not keep track of how many clinical study reports it has released through FOIA, Walsh says. But Doshi and others say such releases are rare, and usually a result of lawsuits or the threat of legal action. In 2011, Doshi requested clinical study reports for Tamiflu, an antiviral medication used to treat the flu. “Eight years later, I think those requests are still alive,” he says now. “I don’t remember getting a denial. They just sit.”

Outside researchers can appeal to companies directly for access to clinical study reports. At least 24 of PhRMA’s 35-member companies have signed on to its six-year-old **principles** for “responsible clinical trial data sharing,” committing to the release of synopses of clinical study reports for approved medicines and to considering requests for data and the full reports from “qualified” medical and scientific researchers who submit research proposals.

But researchers are concerned they won’t be granted access if companies are not comfortable or sympathetic to their proposals, Herder says. And the companies control the amount of redaction.

The British-based pharmaceutical company GlaxoSmithKline (GSK) has gone further than most in providing public access to its data. In 2013, the company began posting clinical study reports through its own online portal, **Clinical Study Register**, which is open to the public. “We have published over 2,500 clinical study reports and nearly 6,000 summaries of results -- both positive and negative -- from our trials on Clinical Study Register,” Andrew Freeman, director and head of medical policy, said in an emailed statement. “GSK is leading the industry in transparency.”

Even so, GSK controls the level of redaction, says Jefferson of Cochrane, who tried to use clinical

study reports posted on the company's portal for a systematic review of human papillomavirus vaccines. "Important aspects, for instance the narratives of serious adverse events — those are all blocked out. Big black boxes," he says. "So they are of moderate use."

Meanwhile, many researchers do not realize that Health Canada and the EMA are making clinical study reports available. An **online survey** of 160 researchers around the world who conduct systematic reviews found that 133 "had never considered accessing regulatory data" and 117 of those 133 "were not aware (or were unsure) of where to access such material." They continue to rely on the limited data in journal articles and other published literature, Herder says.

"Transparency is wonderful in theory, but unless people actually do the work of getting data and independently analyzing it, transparency is window dressing," he says.

This story originally appeared on **Undark**. *It has been slightly modified to reflect* Spectrum's *style*.