

Governance of conflicts of interest in postmarketing surveillance research and the Canadian Drug Safety and Effectiveness Network

LORRAINE E FERRIS, TRUDO LEMMENS

Lorraine E Ferris, PhD, LLM, is a professor at the Dalla Lana School of Public Health, University of Toronto, a senior scientist at the Clinical Epidemiology Unit, Sunnybrook Health Sciences Centre, and a senior scientist at the Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada. **Trudo Lemmens**, LicJur, LLM, DCL, is an associate professor at the Faculties of Law and Medicine, University of Toronto.

Funding: Trudo Lemmens is supported by a Social Sciences and Humanities Research Council grant, “Promoting Integrity in Medical Research: the Janus Face of Regulation.”

Competing interests: None declared.

Correspondence: Dr. Lorraine E. Ferris, Dalla Lana School of Public Health, 500 University Ave., Ste. 160, Toronto ON M5G 1V7; lorraine.ferris@utoronto.ca

THERE HAS BEEN SURPRISINGLY LITTLE RESEARCH in the public domain on the long-term safety and effectiveness of postmarket drugs—drugs that have been approved by regulators and are being used by consumers—even though this information is needed by regulators, policy-makers, health care providers and consumers. The establishment in Canada of the national Drug Safety and Effectiveness Network (DSEN)¹ and its first call for applications for postmarketing studies are therefore positive developments for consumer and patient safety. Established and largely administered by the Canadian Institutes of Health Research (CIHR), the DSEN will fund independent and scientifically rigorous real-world studies on the safety and effectiveness of postmarket drugs in Canada and will connect to the research being conducted through a virtual network of Canadian centres of excellence in postmarketing pharmaceutical research. These centres will have a common research agenda and strategic direction set by a DSEN steering committee. In addition, the DSEN will assist in coordinating a national research agenda based on decision-makers’ priorities. The federal government has made a financial commitment to the DSEN of \$32 million over the first 5 years and \$10 million per year thereafter.¹

We believe it is essential for the DSEN to secure the public’s confidence quickly, which has been shaken in recent years by a series of scandals related to postmarket drugs. Many medical journals made urgent calls for better reporting of adverse events, more active postmarketing surveillance and better designed studies^{2,3} particularly in the wake of the highly publicized withdrawal from the market of rofecoxib (Vioxx),^{4,5} a now infamous drug that has been associated with major adverse events, including myocardial infarctions or strokes in “tens of thousands of patients.”⁴ Other controversies include the promotion of hormone replacement therapy⁶ and the off-label promotion of arthritis drug valdecoxib (Bextra), epilepsy drug gabapentin (Neurontin), and the schizophrenia drug olanzapine (Zyprexa), the latter three resulting in criminal prosecutions, fines and settlements of hundreds of millions of dollars, and, in the case of valdecoxib, a record-setting settlement of US\$2.3 billion.^{7–9}

In Canada, drug manufacturers are required to report postmarket adverse drug reactions. They are not, however, currently required to conduct new efficacy or safety studies, or studies on therapeutic effectiveness.¹⁰ In Canada and the United States, questions have been raised about the legislative authority of drug regulatory agencies to mandate such studies. In the US, before the Food and Drug Administration (FDA) Amendments Act of 2007,¹¹ it was unclear whether the FDA had the legislative or regulatory authority to request postmarketing surveillance studies¹² other than in cases where a drug had received accelerated approval.¹³ Unfortunately, despite encouragements to conduct postmarket studies and to comply with postmarket commitments, there is evidence that drug manufacturers fail to do so and that drug regulators are not adequately monitoring postmarketing surveillance commitments.^{4,13,14} In Canada, Health Canada believes it does not have the regulatory authority to explicitly impose postmarketing studies as a condition for further sales of a pharmaceutical product.¹⁰ To address this and other issues related to drug regulation, Health Canada has been working for some years on a progressive licensing framework that, among other things, will give the government authority to require drug manufacturers to conduct postmarket studies and to submit the resulting data for review.^{10,15,16}

As important as a progressive licensing framework will be to Canada, it is crucial to keep in mind that many have questioned the wisdom of relying on drug manufacturers to conduct postmarketing studies of their own products.¹⁷ Studies indicating a statistical correlation between study outcomes and funding source, reports of

misleading selection of trial designs, and the exposure of instances of data suppression, data misrepresentation, ghost authorship or research articles by industry-funded writers and other related practices have added fuel to this concern.^{18,19}

Enter the DSEN. Although drug manufacturers will continue to have mandatory obligations to report adverse drug reactions (and possibly in the future to conduct postmarket studies), the DSEN will fund “independent research on the safety and effectiveness of post-market drugs.”²⁰ Having CIHR operate the DSEN could strengthen public confidence in the independence of the network since CIHR is not involved in drug approvals—as Health Canada is—and has no direct financial interest in drug development—as pharmaceutical companies have. CIHR has the status and connections to secure the commitment of qualified researchers who are independent from the products and the drug manufacturers. In their 2006 commentary on reforming US drug regulation, Ray and Stein¹⁹ call for the establishment of an independent, specialized centre for postmarketing studies with a mandate to promote the unfettered conduct of postmarketing studies by independent researchers. Before amendments were made to the US Food and Drug Act in 2007, several commentators argued that there was a need for a fully independent US agency or centre for postmarket studies.^{19,21} This would avoid the conflict that arises when the agency that approves new drugs is also in charge of conducting postmarket studies on those same drugs, the results of which can lead to their withdrawal and could suggest a failure in the approval process. However, although the FDA Amendments Act (2007)¹¹ gave the FDA authority to, among other things, order drug manufacturers to conduct postmarketing studies, it stopped short of creating an independent agency for postmarketing drug trials or imposing fully independent post-marketing surveillance research.

We believe that a fully independent agency with post-marketing surveillance as its core mandate would be ideal, but having the CIHR operate the DSEN moves Canada forward, provided that some conditions are fulfilled. Box 1 provides a summary of our key recommendations.

First, a DSEN good governance framework (characterized by the existence of a well-defined operating structure, clear lines of operational accountability and high standards for integrity and openness) must be instituted that is based on an effective approach for avoiding and mitigating conflicts of interest. Dealing appropriately with conflict of interest will provide researchers with the necessary environment for producing credible, honest, timely and scholarly research that

Box 1: Key recommendations to ensure the independence of the Drug Safety and Effectiveness Network (DSEN)

- The DSEN must institute a good governance framework based on a sound approach to avoiding and mitigating conflict of interest. (See Box 2.)
- The DSEN must have strong and enforceable conflict-of-interest rules for all those involved in DSEN-funded research and its reportage and knowledge translation.
- The DSEN must have strong and enforceable measures to protect its independence and the independence of researchers from influence by Health Canada's Therapeutic Products Directorate and drug manufacturers.
- The DSEN steering committee must not include members who have financial interests in marketed products or have financial ties with those who do.
- The DSEN must be structurally independent from CIHR activities relating to creating and maintaining CIHR–industry partnerships and collaborations.

can withstand academic and public scrutiny. Stringent conflict-of-interest rules and other measures to ensure the independence of researchers are essential in this context because postmarketing surveillance research can have huge financial implications. The potential need to withdraw a blockbuster drug from the market, and potential legal liability related to findings of serious side effects, create serious incentives that may affect behaviour. Stocks in Merck Frosst tumbled by 30% the day after Vioxx was withdrawn from the market, decreasing the company's market value by an estimated US\$26.8 billion; this is a stark reminder of what interests are at stake.²²

Strong and enforceable conflict-of-interest rules for all those involved in the research, its reportage and knowledge translation (e.g., researchers, centres of excellence and their staff), and measures to protect researchers' independence are in our view crucial. Such rules and measures are needed because of the very significant public health implications of this type of research and the reasonable concern that the financial interests of industry sponsors in an already marketed product can lead to significant pressure on investigators, institutions and those working directly under contract with pharmaceutical sponsors. This is not to say that such pressure always affects researcher or institutional behaviour, but it is a reasonable expectation that such pressure can have this impact and can affect public trust.

Our support for CIHR establishing and largely administering the DSEN is also conditional on the expectation that CIHR will be sufficiently funded and strongly independent from both Health Canada's Therapeutic Products Directorate and drug manufacturers since this is crucial for a public funding agency that has a mandate through the DSEN to promote independent drug

surveillance research. The commercialization mandate embedded within the statutory role of CIHR and the growing emphasis on CIHR–industry partnerships do, in this context, create a tension. A major step forward for CIHR would be the adoption of an ethics policy on partnership with the for-profit private sector, as discussed at a 2007 CIHR workshop,²³ which takes into account CIHR’s role with respect to the DSEN.

In the spring of 2009 we presented a governance framework at a DSEN workshop on potential legal and ethical risks²⁴ to address conflict-of-interest issues. We

recommended that the DSEN governance and operational standards should be such that they promote five intertwined principles: transparency and openness, accountability, independence, commitment to scientific integrity, and freedom of action. Boxes 2 and 3 (which are reproduced largely from our presentation) elaborate on the five key principles in the context of the DSEN governance and as applied to DSEN-funded researchers.

Although details of the governance system are not yet available, we did obtain some information about the general oversight structure. The DSEN’s steering committee,

Box 2: Elaboration of the five principles for good governance of the Drug and Safety Effectiveness Network (DSEN)

1. Transparency and openness

Public disclosure of vital network information such as:

- standards for evaluating the network
- governance arrangements
- standards for selecting researchers, staff and centres of excellence
- standards for evaluating researchers
- standards for obtaining and dealing with stakeholders input
- standards regarding sources and use of data
- standard procedure for registration of clinical trials and results reporting
- conflict-of-interest (COI) disclosures by everyone in the network (e.g., officials, researchers)
- procedures for dealing with COI

2. Accountability

Being subject to clear rules of behaviour and being publicly answerable, such as

- existence of clear governance arrangements; partnerships; agreements and policies for protecting academic values and the integrity of the network (including its data)
- efficiency and enforceability of policies and procedures (especially concerning COI, privacy and confidentiality)
- DSEN COI committee: clear authority over COI matters for all DSEN research; uniformity of COI standards for addressing COI across the network for DSEN-related research
- external verification and answerability: registering trials; publishing results independently and within a specific period
- accountability to CIHR
- accountability of centres of excellence to central DSEN administration

3. Independence

Autonomy from stakeholders, such as

- autonomy from commercial influences
- arm’s length from regulatory authorities in areas such as governance; budget; setting policies and enforcing them (especially COI and confidentiality); research priorities, selecting researchers; evaluating network officials and researchers; interpreting data and reporting
- elements: budgetary “independence” (medium- to long-term security); structural and human resources independence
- clear rules about representation and conflicts of interest of public stakeholders
- commitment to public interest promotion with protection against inappropriate capture by special interest groups

4. Commitment to scientific integrity

Dedication to scientific honesty, such as

- preservation of scientific integrity and academic freedom, including selecting researchers who will have as few conflicts of interest as possible
- access to full data and appropriate control over it
- absence of legal constraints associated with access to data and use of data
- support for the conduct of research that is consistent with academic values: unbiased, truthful and rigorous

5. Freedom of action: de facto and de jure

- ability to act independently from commercial influences and being at arm’s length from regulatory authorities, in the best interests of the public
- absence of constraints associated with potential liability for good faith actions (e.g., insurance, commitment of stakeholders to respecting independence of researchers)
- absence from legal constraints flowing from contracts or arrangements that affect the ability (or the perception of ability) to meet commitments to the **core** principles (transparency and openness, accountability, independence, commitment to scientific integrity, freedom of action)

Box 3: Principles for avoiding and mitigating conflict of interest (COI) among researchers and researchers' host institutions involved with the Drug Safety and Effectiveness Network (DSEN)

1. Transparency and openness

- full disclosure of potential, actual or perceived COI of researcher (and his or her family)
- balance between access to information on COI and the privacy interests of individuals
- creation of transparent rules and processes and reliable oversight of COI

2. Accountability

- avoidance of COI situations if possible
- adherence to network COI policies and procedure
- enforcement of COI rules and sanctions
- introduction of “presumption” that researchers cannot have COI, and clear rules of conduct for when exceptions are appropriate and needed

3. Independence

- monetary (actual, perceived or future) independence and academic independence from commercial influences and remaining at arm's length from regulatory authorities
- procedures to deal with centre of excellence host institution COIs and their potential impact on researcher COI
- role of DSEN in strengthening researcher independence in situations of centre of excellence host institutional COI
- protection of researchers against threat of legal procedures by pharmaceutical sponsors for DSEN-related research

4. Scientific integrity

- research that is consistent with academic values (e.g., remaining impartial and truthful, conducting rigorous evaluations with scientific merit, adhering to protocols, publishing/disseminating findings)
- education and support of DSEN researchers (e.g., education on COI issues and DSEN standards for dealing with them, support of independence of researchers, raising awareness of importance of structural independence)

5. Freedom of action: de facto and de jure

- ability to remain free to conduct research that has scientific integrity and that is consistent with network responsibilities, policies and procedures
- ability to remain free to act in the best interests of the public

which will provide strategic direction to the DSEN and set priorities for research, will be appointed and chaired by Dr. Ian Graham, vice-president of knowledge translation and public outreach at CIHR (Krissy Davidge, DSEN, Ottawa, personal communication, Feb 2010).

There are many stakeholders who have a legitimate and material interest in the DSEN's research priorities, and their involvement can strengthen the DSEN. Thus it is important that the DSEN engage these stakeholders, who include, for example, patient or consumer groups, provincial health ministries, drug manufacturers, Health Canada and other policy-makers. We believe the five key principles should set the stage for stakeholder engagement about research priorities. Although having stakeholders contribute their views about research priorities will help inform the DSEN, membership on the DSEN steering committee should be carefully chosen to avoid situations of conflict of interest. Members of the steering committee should not have financial interests in marketed products or have financial ties with those who do. Although having the DSEN operating from within Health Canada would not have allowed

for adequate independence, it is important that Health Canada provide input about research priorities, which will be possible through DSEN's role in assisting with the coordination of a national research agenda based on decision-makers' priorities. Finally, the DSEN should also be set up so that it is structurally independent within the CIHR from those who are involved in the creation and promotion of CIHR–industry collaboration.

We believe the DSEN and CIHR can play a major role in securing the public's trust in postmarketing studies, but respect for and realization of the five core principles will be vital. The appointment of Dr. Bernard Prigent, vice-president of Pfizer Canada, to CIHR's governing Council—the first pharmaceutical representative to be so appointed^{25–29}—and statements by CIHR president Dr. Alain Beaudet in the context of this appointment, emphasizing the need to intensify collaboration and even to align CIHR's “agenda” and “vision” with the pharmaceutical industry,³⁰ do raise the question whether CIHR remains sufficiently independent from industry to operate the DSEN. As one of us (TL) suggested at a hearing of the House of Commons Standing Committee on Health

related to this appointment, Dr. Beaudet's justifications provided in support of this appointment are worrisome rather than reassuring.³¹ Steven Lewis has remarked on this appointment that "Pfizer has an obvious interest in the flow of CIHR funds to science that may lead to drug development, and an obvious interest in diverting CIHR funds away from science that may reveal the comparative ineffectiveness of one of its drugs or challenge the pharmacological therapeutic paradigm."²⁸ We therefore recommend that CIHR and the minister of health, to whom CIHR reports, carefully evaluate the impact of such appointments and of increased collaboration with industry on the DSEN, and ensure its continuing independence.

We commend the CIHR in co-hosting, with Health Canada, the DSEN workshop on potential legal and ethical risks²⁴ and look forward to the release of the final DSEN governance structure and policy documents to see how they fit with the core principles for building public trust we have described here. Canadians deserve scientifically rigorous real-world studies on the safety and effectiveness of postmarket drugs; these can happen only when those with conflicts of interest are not permitted to unduly influence the DSEN's strategic direction, research agenda, research sponsors or the researchers themselves. The appearance of conflict of interest matters,²⁸ and therefore in terms of promoting public trust it is crucial that the DSEN operate from the core principles of transparency and openness, accountability, independence, commitment to scientific integrity and freedom of action.

Contributors: The authors both participated in the conception, writing, revision and final approval of this article.

REFERENCES

- Health Canada. Government of Canada works to improve knowledge about the safety and effectiveness of drugs [news release]. 2009 Jan 14. Available: http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/_2009/2009_03-eng.php (accessed 2010 May 15).
- Vioxx: lessons for Health Canada and the FDA. *CMAJ* 2005;172(1):5.
- Dieppe P, Ebrahim S, Martin RM, Jüni P. Lessons from the withdrawal of rofecoxib. *BMJ* 2004;329:867–868.
- Topol EJ. Failing the public health—rofecoxib, Merck, and the FDA. *N Engl J Med* 2004;351:1707–1709.
- Graham DJ. COX-2 inhibitors, other NSAIDs, and cardiovascular risk: the seduction of common sense. *JAMA* 2006;296:1653–1656.
- Rossouw JE, Anderson GL, Prentice RL, LaCrox AZ, Koopergerg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288(3):321–333.
- United States Department of Justice. Eli Lilly and Company agrees to pay \$1.415 billion to resolve allegations of off-label promotion of Zyprexa [news release]. 2009 Jan 15. Available: http://www.justice.gov/civil/oci/cases/Cases/Eli_Lilly/Lilly%20Press%20Release%20Final%2009-civ-038.pdf (accessed 2010 May 15).
- Evans D. Pfizer broke the law by promoting drugs for unapproved uses. *Bloomberg.com*. 2009 Nov 9. Available: <http://www.bloomberg.com/apps/news?pid=20601109&sid=a4yV1nYxCGoA> (accessed 2010 May 19).
- United States Department of Health and Human Services. Justice department announces largest health care fraud settlement in its history: Pfizer to pay \$2.3 billion for fraudulent marketing [news release]. 2009 Sep 2. Available: <http://www.hhs.gov/news/press/2009pres/09/20090902a.html> (accessed 2010 May 19).
- Health Canada. Drugs and Health Products. Authority to require post-market studies [discussion paper]. 2007 Apr 4. Available: <http://26448.vws.magma.ca/dhp-mps/homologation-licensing/docs/pma-aac/pma-aac04-eng.php> (accessed 2010 May 19).
- Food and Drug Administration Amendments Act of 2007*, Public Law 110–85, Statutes at Law 121 (September 27, 2007), 823–978.
- Committee on the Assessment of the US Drug Safety System. *The future of drug safety: promoting and protecting the health of the public*. Baciú A, Stratton K, Burke SP, editors. Washington, DC: National Academies Press; 2006. Chapter 5, Regulatory authorities for drug safety; p. 151–176.
- Department of Health and Human Services Office of Inspector General. *FDA's monitoring of postmarketing study commitments*. Publ no OE1-01-04-00390. June 2006. Available: <http://oig.hhs.gov/oei/reports/oei-01-04-00390.pdf> (accessed 2010 May 19).
- US Government Accountability Office. *New drug approval: FDA needs to enhance its oversight of drugs approved on the basis of surrogate endpoints. A report to the Ranking Member, Committee on Finance, U.S. Senate*. Publ no GAO 09–866. Washington (DC): GAO; 2009. Available: <http://www.gao.gov/new.items/do9866.pdf> (accessed 2010 May 19).
- Health Canada Drugs and Health Products. The use of post-market commitments [discussion paper]. Available: <http://26448.vws.magma.ca/dhp-mps/homologation-licensing/docs/condition/condition01-eng.php> (accessed 2010 May 19).
- Health Canada Drugs and Health Products. Addressing unfulfilled post-market clinical commitments [discussion paper]. Available: <http://26448.vws.magma.ca/dhp-mps/homologation-licensing/docs/condition/condition02-eng.php> (accessed 2010 May 19).
- Fontanarosa PB, Rennie D, DeAngelis CD. Postmarketing surveillance—lack of vigilance, lack of trust. *JAMA* 2004;292(21):2647–2650.
- Lemmens T. Leopards in the temple: restoring integrity to the commercialized research scene. *J Law Med Ethics* 2004;32(4):641–657.
- Ray WA, Stein CM. Reform of drug regulation—beyond an independent drug-safety board. *N Engl J Med* 2006;354:192–201.
- Canadian Institutes of Health Research. Drug Safety and Effectiveness Network implementation progress August 2009; 2009 Sept 1. Available: <http://www.cihr-irsc.gc.ca/e/40126.html> (accessed 2010 May 19).
- Furberg CD, Levin AA, Gross PA, Shapiro RS, Strom BL. The FDA and drug safety: a proposal for sweeping changes. *Arch Intern Med* 2006;166:1938–1942.
- Rotthoff KW. Product liability litigation: an issue of Merck and lawsuits over Vioxx. Seton Hall Public Law Research Paper No. 1151271. Available: <http://ssrn.com/abstract=1151271> (posted 2008 June 28; revised 2009 Jan 24; accessed 2010 May 19).

23. Ethics policy on CIHR partnerships with the for-profit private sector; 2007 March 19–20; Ottawa. Canadian Institutes of Health Research Workshop.
24. Drug Safety and Effectiveness Network Workshop on Potential Legal and Ethical Risks; 2009 March 6; Toronto. Canadian Institutes of Health Research.
25. Canadian Institutes of Health Research. Bernard Prigent, MD, MBA. 2009 Oct 5. Available: <http://www.cihr-irsc.gc.ca/e/40472.html> (accessed 2010 May 19).
26. Silversides A. Appointment of Pfizer executive to CIHR stirs controversy. *CMAJ* 2009;181(11):E256–257.
27. Ghali W, Kendall C, Palepu A. Pharmaceutical industry representation on CIHR's governing council. *Open Med* 2010;4(1):E26–27.
28. Lewis S. Neoliberalism, conflict of interest, and the governance of health research in Canada. *Open Med* 2010;4(1):E28–30.
29. Baylis F. An intractable conflict of interest. In: The Mark [online forum]; Toronto; 2009 Dec 2. Available: <http://www.themark-news.com/articles/727-an-intractable-conflict-of-interest> (accessed 2010 May 19).
30. Canada. Parliament. House of Commons Standing Committee on Health. Evidence of Proceedings, meeting no. 47, November 30, 2009. Available: <http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=4275165&Language=E&Mode=1&Parl=40&Ses=2>.
31. Canada. Parliament. House of Commons Standing Committee on Health. Evidence of Proceedings, meeting no. 49, December 7, 2009. Available: <http://www2.parl.gc.ca/HousePublications/Publication.aspx?DocId=4302528&Language=E&Mode=1&Parl=40&Ses=2>.

Citation: Ferris LE, Lemmens T. Governance of conflicts of interest in postmarketing surveillance research and the Canadian Drug Safety and Effectiveness Network . *Open Med* 2010;4(2):123-28.

Published: 1 June 2010

Copyright: *Open Medicine* applies the Creative Commons Attribution Share Alike License, which means that authors retain copyright of their work and that anyone is able to freely copy, distribute, transmit or adapt the work as long as all adapted or derivative work is distributed under the same or similar licence to this one and all derivative or non-derivative work is attributed to the author and to *Open Medicine* as specified by the author or *Open Medicine* but in no way that suggests that the author or *Open Medicine* endorses the work or how it is used. Any of these conditions can be waived with permission from the copyright holder. These conditions do not negate or supersede fair use laws in any country. For more information, please see our Creative Commons Attribution ShareAlike 2.5 Canada Licence.
