

DECREASING THE DATA DEFICIT: IMPROVING POST-MARKET SURVEILLANCE IN PHARMACEUTICAL REGULATION

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The drug regulatory system is currently largely based on market-entry review of safety and efficacy data and involves only very limited post-market review. Failures in the industry-controlled production of pre-market data and the lack of solid post-market surveillance contribute significantly to highly problematic drug prescription and consumption practices, which have become a very serious public health concern. In this paper, we first discuss how historically grown drug regulations have contributed to the development of industry control over clinical trials, which is one of the key factors behind the limits of pre-market evidence. We then explore some problematic aspects related to the fixation of the drug approval system on pre-market activities, including the lack of good “real-world” evidence on drug safety; the lack of comparative evidence on patient benefit between different drugs; the lack of evidence of the safety and efficacy of off-label prescribed drugs; and the inadequate reporting of adverse drug reactions (ADRs). We argue that a more rigorous and intense post-market surveillance system could counterbalance, at least in part, the distorted situation created by the regulatory reliance on pre-market, industry-produced clinical trials data. In particular, we advocate for improvements to the current ADR reporting system, more explicit requirements for both comparative effectiveness studies and post-market clinical research in real-world settings, the promotion of transparency of pharmaceutical data, and insulating clinical research from industry control.

Le système réglementaire des médicaments se base actuellement en grande partie sur l'étude des données de sécurité et d'efficacité au point d'entrée sur le marché, mais ne comporte qu'une étude très restreinte après l'entrée sur le marché. Des défauts dans la production de données avant l'entrée sur le marché, entreprise par l'industrie même, et l'absence de surveillance appréciable après l'entrée sur le marché contribuent de façon importante à des pratiques très problématiques de prescription et de consommation des médicaments. Ces pratiques sont devenues un problème de santé publique très grave. Dans cet article, nous étudions d'abord comment la réglementation des médicaments développée à partir d'antécédents historiques a contribué au développement du contrôle par l'industrie pharmaceutique des essais cliniques. Ceci est l'un des facteurs essentiels qui explique les limites des données prélevées avant l'entrée sur le marché. Nous abordons ensuite les aspects problématiques de la fixation du système d'autorisation des médicaments sur les activités avant l'entrée sur le marché, y compris : l'absence de données réelles sur la sécurité des médicaments; l'absence de données comparatives par rapport aux avantages de différents médicaments pour les patients; l'absence de données sur la sécurité et l'efficacité des médicaments prescrits pour des usages non autorisés; et le rapport inadéquat des effets indésirables des médicaments (EIM). Nous soutenons qu'un système de surveillance après l'entrée sur le marché plus rigoureux et intense pourrait compenser, du moins en partie, la situation déformée qu'a engendrée la dépendance réglementaire sur les données basées sur des essais cliniques conduits par l'industrie avant l'entrée sur le marché. En particulier, nous prônons l'amélioration du système actuel de rapport des EIM, des exigences plus explicites pour les études sur l'efficacité comparative et pour la recherche clinique après l'entrée sur le marché dans un contexte réel, la promotion de la transparence dans les données de recherche, et le cloisonnement de la recherche clinique du contrôle par l'industrie.

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Introduction

The drug approval system in industrialized countries is generally divided into two distinct phases: a pre-market phase and a post-market authorization phase. The pre-market phase is characterized by substantial investments in clinical trials aimed at providing data demonstrating the safety and efficacy of a product. Subsequently, in the post-market phase, drugs are generally perceived by both the medical community and the public at large to be safe and effective. In this phase, drug companies rarely undertake additional studies to assess the safety and efficacy of the products in the real-life context in which these drugs are then consumed.¹

To date, the focus of drug regulation, certainly in Canada, has primarily been on pre-market activities and on ensuring that products entering the market fulfill certain basic requirements with respect to safety and efficacy. Unfortunately, lay people—but also to a large degree those involved in the regulation, prescription, use, and funding of pharmaceutical products (including health care professionals)—ignore the limitations of the data produced in pre-market clinical trials. These trials are conducted under the control of an industry that has a vested and significant financial interest in showing that the products tested in these trials work. Yet the approval of drug products by regulatory agencies such as Health Canada is easily taken as a firm confirmation of their safety and value.

As we explain below, the drug regulatory system that has developed throughout the twentieth century, while obviously intended to improve the safety and efficacy of pharmaceutical products, has also had perverse side effects. This system has strengthened the dominant position of industry over the creation of clinical trials data; it has created a false assurance of safety and efficacy by the very fact of approving the marketing of these drugs on the basis of the submitted data; and finally, it has enabled industry, which is largely in control of the production and publication of the results of clinical trials, to use this false assurance as a marketing tool. At the same time, the pharmaceutical industry has at this point little inherent interest in critically evaluating or questioning whether the data produced in pre-market testing for the purpose of drug approval is sufficient or provides the most meaningful information. In fact, as we will argue, the opposite is often true.

We will not discuss in detail in this article the various components of industry control over pharmaceutical research, product development, and distribution of information. Instead, we want to explore, with an emphasis on Canadian developments, how a shift toward better post-marketing

¹ See H-G Eichler et al, “Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval” (2012) 91:3 *Clinical Pharmacology & Therapeutics* 426.

surveillance could counterbalance, at least in part, the distorted situation created by our reliance on pre-market clinical trials data produced under the control of industry.

The importance of correcting the knowledge deficit resulting from industry control over data and from the lack of post-market data cannot be overestimated. Bad information leads to bad health care practices, often resulting in serious injuries and death. The wide-ranging health risks associated with industry manipulation and misrepresentation of data, combined with aggressive marketing practices, have been highlighted, particularly in the last decade, in a panoply of media reports and publications.² As these publications and reports highlight, a remarkably high number of serious injuries or deaths are linked to these practices, which makes it increasingly hard to understand the so far very timid response by regulators and governmental decision makers. The extent of the control of industry over scientific data also has another important consequence that negatively affects potential legal responses (for example, tort law) to this problem: by avoiding the collection of evidence about adverse effects of pharmaceutical products that are currently on the market, or by directly manipulating the presentation of data in the scientific literature, industry can shield itself more easily from potential liability for deficiencies associated with its products. The powerful influence, if not control, of industry over the production of scientific evidence thus also impacts on legal tools that could otherwise be used to deter or provide compensation for injury resulting from defective products.³ The legal community should therefore also start

² For recent detailed discussions, see e.g. Peter C Götzsche, *Deadly Medicines and Organised Crime: How Big Pharma Has Corrupted Healthcare* (London: Radcliffe, 2013); Ben Goldacre, *Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients* (London: Fourth Estate, 2012); Ray Moynihan & Allan Cassels, *Selling Sickness: How the World's Biggest Pharmaceutical Companies Are Turning Us All into Patients* (New York: Nation Books, 2005); Terence H Young, *Death by Prescription: A Father Takes On His Daughter's Killer: The Multi-Billion-Dollar Pharmaceutical Industry* (Toronto: Key Porter Books, 2009) (with a focus on Canada). See also David Healy, *Pharmageddon* (Berkeley: University of California Press, 2012); Carl Elliott, *White Coat Black Hat: Adventures on the Dark Side of Medicine* (Boston: Beacon Press, 2010); Trudo Lemmens & Ron A Bouchard, "Regulation of Pharmaceuticals in Canada" in Jocelyn Downie, Timothy Caulfield & Colleen M Flood, eds, *Canadian Health Law and Policy*, 3d ed (Markham, Ont: LexisNexis Canada, 2007) 311 at 311–14; Trudo Lemmens, "Leopards in the Temple: Restoring Scientific Integrity to the Commercialized Research Scene" (2004) 32:4 *JL Med & Ethics* 641 [Lemmens, "Leopards"]; Trudo Lemmens, "Pharmaceutical Knowledge Governance: A Human Rights Perspective" (2013) 41:1 *JL Med & Ethics* 163 [Lemmens, "Pharmaceutical Knowledge Governance"]; Trudo Lemmens & Candice Telfer, "Access to Information and the Right to Health: The Human Rights Case for Clinical Trials Transparency" (2012) 38:1 *Am J L & Med* 63.

³ See Gary Edmond, "Supersizing *Daubert Science for Litigation* and Its Implications for Legal Practice and Scientific Research" (2007) 52:4 *Vill L Rev* 857 (Edmond is one of the only authors who has explicitly warned about the impact of industry control over sci-

to take much more seriously the consequences of the gaps in the scientific data production processes, as they compromise the integrity of the legal system itself.

This paper provides recommendations to improve, within the contours of the current Canadian drug regulatory system, the ways in which data is being produced and distributed. We begin by describing the historical development of industry control over clinical trials, followed by a brief overview of the limitations of pre-market clinical trials. Subsequently, we argue that the inadequacy of the safety and efficacy data created at the pre-market stage only increases the importance of enhanced surveillance activities during the post-market phase. Expanded post-market surveillance is necessary in order to combat a host of problems, including the lack of good evidence on long-term safety and comparative effectiveness; the need for improved adverse event reporting; and the phenomenon of off-label prescribing. We will briefly highlight these issues and discuss some avenues for improvement. Finally, we highlight the importance of promoting the transparency of clinical trials, which constitutes a crucial condition for correcting the failure in data production at both the pre-market and post-market stages.

I. Challenges in Pre-Market Evidence Development

A. *Historical Developments in Requirements for Market Entry*

There is a historical reason for the focus of the drug regulatory system on the pre-market stage and the more limited attention to what happens after drugs have entered the market. Pharmaceutical regulations were first introduced in the late nineteenth century, a time of untrammelled and rapidly expanding market capitalism. These regulations aimed to establish a regulatory barrier against the mass marketing of often highly toxic products of the so-called “patent medicines” industry—an industry of home-brew quackeries that was rapidly expanding at that time, partly as a result of new mass media technology and improved transportation infrastructure.⁴ As Philip J. Hilts describes in his history of the US Food and Drug Administration (FDA), this patent medicines industry had

ence for tort law and litigation). See also Simon Stern & Trudo Lemmens, “Legal Remedies for Medical Ghostwriting: Imposing Fraud Liability on Guest Authors of Ghostwritten Articles” (2011) 8:8 PLoS Medicine 1 [Stern & Lemmens, “Legal Remedies”].

⁴ See Lemmens & Bouchard, *supra* note 2 at 314–15. For a good historical overview of the development of drug regulation in the US, see Philip J Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Albert A Knopf, 2003); Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton: Princeton University Press, 2010).

gained a reputation for aggressively promoting often highly toxic or seriously addictive products for the treatment of a variety of ailments, including serious diseases.⁵ Numerous deaths, serious injuries, and high rates of addiction were associated with several of these products. The goal of the first regulations was thus to provide some, albeit fairly limited, governmental control at market entry to ensure that uninformed consumers were protected against manifestly dangerous products. State control over the sale of such products was an exceptional step at the margins of the market, aimed at preventing market excesses that threatened public safety.

Later controversies throughout the twentieth century resulted in piecemeal extensions of regulatory review and additional regulatory requirements. These controversies took place also in the context of significant changes to the pharmaceutical development and production process and to the overall nature of the pharmaceutical industry, particularly since the middle of the twentieth century. It is fair to state that the more science-based pharmaceutical industry that began its gradual development in the 1940s was quite distinct from the patent medicines industry of the earlier era. Daniel Carpenter describes how various interacting political, scientific, medical, and market changes contributed to a gradual shift in pharmaceutical policy in the United States, which in turn influenced pharmaceutical policies in other countries. Pharmaceutical policy became more sophisticated, based on detailed interactions and discussions between regulatory agencies and pharmaceutical companies. Products were increasingly submitted to more detailed procedural scrutiny.⁶ This culminated in the formal legislative introduction of a general efficacy requirement in the 1960s, in the wake of the Thalidomide disaster.⁷

⁵ During the Prohibition era, it is interesting to note that many “medicines” were purchased for their alcohol or heroin content. See Hiltz, *supra* note 4 at 23–27.

⁶ See Carpenter, *supra* note 4.

⁷ The drug Thalidomide, which was marketed in forty-six countries around the world, was touted as a wonder drug for the treatment of morning sickness in pregnant women. The drug had, however, catastrophic side effects. It caused phocomelia (or “seal limbs”, a serious malformation of the limbs) in an estimated ten thousand newborns. Even though the tragedy revealed, in the first place, serious problems with drug safety review, it also significantly augmented overall public support for more rigorous review of both drug safety and efficacy.

Carpenter argues that many historical accounts of the development of drug regulations fail to appreciate that the formal introduction of an efficacy requirement was not such a radical shift, but was the culmination of a gradual process that had already started more informally in the 1940s (*ibid* at 119–20, 150–51). For a brief overview of the Canadian history, see Health Canada, “Brief History of Drug Regulation in Canada” (11 April 2007), online: Health Canada <www.hc-sc.gc.ca> [Health Canada, “Brief History of Drug Regulation”].

In the United States, the introduction of the efficacy requirement with the Kefauver Harris amendments to the FDA was accompanied by the Drug Efficacy Study (DES), a historically unique and massive regulatory initiative to evaluate, particularly from an efficacy perspective, the pharmaceutical products already on the market at the time.⁸ Between 1966 and 1969, the FDA organized the evaluation of approximately four thousand marketed products, including many top-selling drugs, with support from many academic specialists in clinical pharmacology and medicine.⁹ The outcome of the DES constitutes probably one of the most impressive debunkings of the “market-efficiency myth” in the context of the marketing of pharmaceutical products. Jeremy A. Greene and Scott H. Podolsky indicate that by the 1970s, the evaluation program had deemed six hundred of the drugs to be ineffective.¹⁰ This clearly suggests that market forces alone ensure neither that only effective products remain on the market nor that reliable information on the most effective products becomes easily available as a result of market competition. Yet the very important lessons to be heeded from this study appear to be lost on many commentators.

Notwithstanding the DES and the worldwide introduction of efficacy requirements in drug regulation, it is fair to state that this did not result in a more sophisticated assessment of the safety and efficacy of drugs once they entered the market. Neither did it result in a systematic comparative review of the merits of new drugs as part of the drug approval process. To this day, pharmaceutical regulations in both the US and Canada basically still only require drug manufacturers to provide limited evidence that a drug has some efficacy, based on a few so-called pivotal trials.¹¹ The division of labour within the drug regulatory system has also remained largely the same. Notwithstanding increased scrutiny and growing interaction

⁸ In his impressive analysis of the historical development of the regulatory power of the US FDA, Daniel Carpenter points out that even before the formal introduction of this efficacy requirement, FDA practice had developed in such a way that the regulator did evaluate efficacy in the context of its safety assessment, rightly arguing, for example, that an ineffective drug inherently raises safety concerns (Carpenter, *supra* note 4 at 149–56, 188–94).

⁹ *Ibid* at 345–57.

¹⁰ “Reform, Regulation, and Pharmaceuticals: The Kefauver-Harris Amendments at 50” (2012) 367:16 *New Eng J Med* 1481 at 1482. See generally *The Drug Efficacy Study of the National Research Council’s Division of Medical Sciences, 1966–1969*, online: National Academy of Sciences <www.nasonline.org> (the publicly available results of the study). According to Hilts, the 1969 FDA final report concluded that “about 7 percent of the drugs reviewed were completely ineffective for every claim made. Another 50 per cent of drugs were judged effective to some degree on some claims and ineffective on others” (*supra* note 4 at 176).

¹¹ See Lemmens & Bouchard, *supra* note 2 at 320–25.

between regulatory agencies and producers, the latter have remained in control of both the production of the pharmaceutical product and the accompanying primarily safety-related data. Regulatory agencies have exercised a marginal level of control based on information submitted by the industry.

B. Issues in the Production of Clinical Trials Data

The gradually increasing demand for data by regulatory agencies was obviously intended to enable a more informed regulatory decision at market entry. But it has also had an interesting side effect: it has strengthened the dominant position of industry over the overall production of scientific data. In the long run, an increasingly demanding regulatory environment and the mounting level of data required from pharmaceutical producers has contributed to a decline in the independence of data gathering and the rise of clinical research led by those with a vested interest in the approval and promotion of new drug products. The blockbuster model of pharmaceutical development that has evolved since the 1960s—with often phenomenal profits associated with the sale of a product during the life of its patent—has increased the financial pressure to collect the data required for regulatory approval as fast as possible, as any delay under this model results in a potential loss of thousands, if not millions, of dollars in sales revenue each day. This growing request for data, combined with the pressure for expedient and efficient data gathering, has led to the development of a specialized service industry, the clinical trials industry, which has as its exclusive mandate to assist the producers of pharmaceutical products with the collection of data needed for regulatory approval.

Clinical trials increasingly became the nearly exclusive business of specialized contract research organizations (CROs), the key players within this clinical trials industry. The demand for increasingly detailed clinical trials data sets needed for regulatory approval resulted in more industrial data production processes, organized by CROs with direct contractual commitments to pharmaceutical companies. CROs could conduct these trials more efficiently and collect data more quickly than academic medical centres, which had originally played a more important role in the conduct of clinical drug trials, and which arguably were originally more independent from industry. Particularly from the 1980s onward, clinical trials gradually moved away from academic medical centres to these specialized CROs,¹² which offer the pharmaceutical industry assistance with all the

¹² See Robert Steinbrook, “Gag Clauses in Clinical-Trial Agreements” (2005) 352:21 *New Eng J Med* 2160 at 2161; Philip Mirowski & Robert Van Horn, “The Contract Research

services surrounding the increasingly “industrialized” production of data: designing the clinical trials, obtaining research ethics approval,¹³ recruiting human research subjects, collecting and analyzing data, and, often with the assistance of other specialized entities such as medical communications agencies,¹⁴ writing up the trial results and strategically publishing and presenting the data. Academic investigators and academic clinical research centres remain to some degree involved in the conduct, analysis, and publication of clinical trials, but they clearly no longer play a leading role. In addition, to the extent that they are still involved in clinical drug trials, academic medical centres have become much more dependent on corporate funding,¹⁵ with various governmental funding agencies also aggressively promoting industry co-funding for various forms of research.¹⁶ Academic investigators often function as expert advisors, or are recruited as key opinion leaders, sometimes primarily to provide lectures touting the benefits of new products. Others contribute to the recruitment of patients in multi-centre clinical trials without having any real control over the final analysis of the full data. There is also a significant body of evidence suggesting that academic authors are frequently only involved as “guest authors” after all the research has been conducted and the results

Organization and the Commercialization of Scientific Research” (2005) 35:4 *Social Studies of Science* 503 at 505.

- ¹³ Note that in many jurisdictions, research ethics review itself has gradually been integrated as part of the new research service industry. See the debate about the desirability of research ethics as a commercial service in Ezekiel J Emanuel, Trudo Lemmens & Carl Elliot, “Should Society Allow Research Ethics Boards to Be Run As For-Profit Enterprises?” (2006) 3:7 *PLoS Medicine* 941; Trudo Lemmens & Benjamin Freedman, “Ethics Review for Sale? Conflict of Interest and Commercial Research Review Boards” (2000) 78:4 *The Milbank Quarterly* 547.
- ¹⁴ See Sergio Sismondo, “Ghosts in the Machine: Publication Planning in the Medical Sciences” (2009) 39:2 *Social Studies of Science* 171.
- ¹⁵ Industry funding of—and consequent influence over—research conducted in academic centres has increased significantly in recent decades. Sheldon Krinsky reports that in the US, corporate contributions to research and development in academic institutions increased by 875 per cent between 1980 and 2000 (*Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* (Lanham: Rowman & Littlefield, 2003) at 79–81).
- ¹⁶ See *ibid.* For more discussion of Canadian developments, see Janet Atkinson-Grosjean, *Public Science, Private Interests: Culture and Commerce in Canada’s Networks of Centres of Excellence* (Toronto: University of Toronto Press, 2006); Jocelyn Downie & Matthew Herder, “Reflections on the Commercialization of Research Conducted in Public Institutions in Canada” (2007) 1:1 *McGill JL & Health* 23; Trudo Lemmens, “Commercialized Medical Research and the Need for Regulatory Reform” in Colleen M Flood, ed, *Just Medicare: What’s In, What’s Out, How We Decide* (Toronto: University of Toronto Press, 2006) 396.

have been prepared for publication by scientific writers working directly for industry.¹⁷

In this new clinical trials environment, trials not only provide the data necessary for regulatory approval, they have also become the near-exclusive source of knowledge about new products. Clinical trials have thus gradually come to serve a double purpose: enabling regulatory approval, while at the same time providing data that could be used for the further promotion of an approved product. Strategically placed in leading medical journals, the data—or at least the data useful for promotional purposes—collected, organized, and written up in close collaboration between the pharmaceutical industry, CROs, and medical communications agencies, bestows upon pharmaceutical products the necessary credentials to boost prescriptions and sales.

Since the 1980s, other factors have contributed to the growing importance of clinical trials data within the context of medicine and health care practice.¹⁸ Among the most significant is the growing emphasis on evidence-based medicine (EBM). The EBM paradigm gained in strength in parallel with the further development of more sophisticated statistical clinical trials methodologies. A detailed discussion of these developments exceeds the scope of this paper, but it is worth emphasizing that in the context of EBM, the evidence produced in clinical trials increased in importance to the detriment of other sources of evidence, such as reports of individual experiences by clinicians in medical practice.¹⁹ The published results of clinical trials conducted by CROs for pharmaceutical companies became the most important source of information influencing physician prescription behaviour, either directly through their reporting in the scientific literature, or indirectly through the influence of these reports on clinical practice guidelines developed by experts in the field based in part on a detailed analysis of the scientific literature and available meta-analyses.

There are, however, serious limitations associated with the publication of clinical trial results, limitations that undermine their overall reliability. There is little control, other than the peer-review system—which is increasingly criticized for its failure to prevent the publication of flawed

¹⁷ See Lemmens, “Leopards”, *supra* note 2; Stern & Lemmens, “Legal Remedies”, *supra* note 3.

¹⁸ For a more detailed discussion of these factors, see Lemmens, “Pharmaceutical Knowledge Governance”, *supra* note 2 at 173–74.

¹⁹ See Healy, *supra* note 2 at 129–94.

research²⁰—over how these data are presented in the medical literature, which, as several authors have discussed in detail, has often become a marketing conduit for pharmaceutical products.²¹

C. Understanding the Interests of Industry

The pharmaceutical industry has little inherent interest in evaluating or questioning whether the production of pre-approval data is sufficient or provides the most meaningful information; this is not what the industry is asked to do, and there is no incentive for industry to do so once a drug receives market approval. In fact, the contrary is true: drug producers often benefit from the deficit of data on drug safety and efficacy caused by, first, a lack of transparency and of rigorous control during the pre-market phase, and subsequently, a lack of post-market surveillance. This is not to say that there are no circumstances under which the pharmaceutical industry may have significant incentives in evaluating its product in the post-market phase. There may be concerns that a failure to follow-up specific preliminary indicators could result in future lawsuits. Companies may want to expand the approved indications in drug labelling. Additional post-market studies may also be demanded by payers before reimbursing a drug product. More negatively, pharmaceutical companies may also use large phase III and phase IV trials as marketing tools. These trials can boost the status of products and accustom physicians and patients to the new drugs even before they hit the market.²²

Yet there are various reasons to be skeptical about the reliability of post-market data produced by drug manufacturers. The most important one is that contrary to dominant market ideology, market actors do not always have an interest in exposing the inadequacy of competitors' products, particularly not when the industry as a whole benefits from artificially created needs. No pharmaceutical company will, for example, enthusiastically expose that competitors' anti-depressants are too widely used for often very minor conditions, that antibiotics are overprescribed, and that the use of cholesterol-lowering drugs may not be the best or the only way to reduce the risk of heart disease. Even if companies have, in theory, an interest in showing that their own products are better than

²⁰ See Richard Smith, "Peer Review: A Flawed Process at the Heart of Science and Journals" (2006) 99:4 *Journal of the Royal Society of Medicine* 178. See also John P A Ioannidis, "Why Most Published Research Findings Are False" (2005) 2:8 *PLoS Medicine* 696.

²¹ See e.g. Sismondo, *supra* note 14.

²² See Lemmens, "Leopards", *supra* note 2 at 645; Carl Elliott, "The Deadly Corruption of Clinical Trials", *Mother Jones* (September/October 2010), online: [Mother Jones <www.motherjones.com>](http://www.motherjones.com).

competing products, they have a shared interest in luring patients into over-consumption. In fact, particularly when a class of medication is not—or is only marginally—effective, producers of these products have a joint interest in avoiding critical analyses. Companies may also sometimes prefer a situation of uncertainty, when it is not so clear which product could turn out to be better in a head-on comparison. They may want to avoid engaging in potentially damaging comparative trials that could affect the status of their own products, since marketing techniques may provide more efficient and more easily controlled means to promote consumption. Moreover, illness tends to render people vulnerable. Particularly when patients are suffering from serious or even life-threatening diseases, they are much more easily manipulated by misinformation and pushed toward overconsumption of pharmaceuticals.²³

It is becoming increasingly clear that the reliance on industry-controlled pre-market data combined with the absence of incentives to conduct reliable post-market surveillance is resulting in serious consequences. In recent decades, the nature of post-market risk has shifted due to the rise of “blockbuster” drugs that are so widely prescribed—and often for the long-term treatment of chronic conditions—that even a minor change in relative risk can result in thousands of adverse reactions.²⁴ As various controversies involving massively prescribed pharmaceuticals have shown, deficiencies during the pre-market phase can create a host of serious problems that escalate rapidly when a drug is widely promoted after it enters the market.²⁵ This may in part explain why serious adverse events appear to have increased in recent decades.²⁶

²³ See the more detailed discussion in Lemmens, “Pharmaceutical Knowledge Governance”, *supra* note 2 at 164–65. An interesting example of the harm caused by increased prescription of pharmaceuticals is the threefold increase in deaths resulting from prescription opioids in the US between 1999 and 2007, which is associated with an increase in opioid prescription rates for chronic pain with causes other than cancer: see Irfan A Dhalla, Navindra Persaud & David N Juurlink, “Facing Up to the Prescription Opioid Crisis” (2011) 343:7823 *British Medical Journal* 569.

²⁴ Between 1998 and 2005, there was an increase in serious adverse drug reactions (ADRs) in the US from 34,966 to 89,842. During the same period, fatal ADRs increased 2.7-fold, a rate four times faster than outpatient prescriptions, placing ADRs among the top ten leading causes of death in the US: see Thomas J Moore, Michael R Cohen & Curt D Furberg, “Serious Adverse Drug Events Reported to the Food and Drug Administration, 1998–2005” (2007) 167:16 *Archives of Internal Medicine* 1752, cited in Mary Wiktorowicz, Joel Lexchin & Kathy Moscou, “Pharmacovigilance in Europe and North America: Divergent Approaches” (2012) 75:1 *Social Science and Medicine* 165 [Wiktorowicz et al].

²⁵ See, for example, the controversy surrounding the widely prescribed pain relief medication Vioxx (see Topol, *infra* note 30).

²⁶ See Wiktorowicz et al, *supra* note 24.

D. The Limitations of Pre-Market Clinical Trials Evidence

Clinical trials primarily detect common and frequently occurring adverse drug reactions; they often miss important reactions that take a long time to develop or that only occur infrequently.²⁷ Importantly, they are conducted under controlled conditions that do not necessarily reflect how a drug will be used in the real world.²⁸ Research subjects in clinical trials receive the drug under direct medical supervision, are not necessarily exposed to other drug products or suffering from underlying diseases,²⁹ and are usually younger, healthier, and less diverse than patients in the real world.³⁰ Further, as will be discussed below, drugs are often prescribed “off-label” to patient and disease groups that were never assessed in clinical trials.³¹

²⁷ “Adverse Reaction Information” (2012), online: Health Canada <www.hc-sc.gc.ca> [Health Canada, “Adverse Reaction Information”].

²⁸ For example, “clinical trials for new drugs are of short duration and are conducted in populations that number from a few hundred to several thousand [patients]; ... most trials exclude the elderly, children, pregnant women, patients with multiple diseases, and those on medications suspected of interaction with the study drug” (Syed Rizwanuddin Ahmad, “Adverse Drug Event Monitoring at the Food and Drug Administration: Your Report Can Make a Difference” (2003) 18:1 *Journal of General Internal Medicine* 57 at 57).

²⁹ See Health Canada, “Adverse Reaction Information”, *supra* note 27.

³⁰ See Richard Gliklich & Christina DeFilippo Mack, “Comparative Effectiveness Research in the Real World” (2009) Q3 *Next Generation Pharmaceutical* 94 at 94. The risk that important safety data only becomes apparent after many people start using the medication is highlighted by the highly publicized market withdrawal of Vioxx. The now infamous drug has been associated with major adverse events, including myocardial infarctions or strokes in tens of thousands of patients (see Eric J Topol, “Failing the Public Health: Rofecoxib, Merck, and the FDA” (2004) 351:17 *New Eng J Med* 1707; David J Graham, “COX-2 Inhibitors, Other NSAIDs, and Cardiovascular Risk: The Seduction of Common Sense” (2006) 296:13 *Journal of the American Medical Association* 1653). Another major controversy was the promotion of hormone replacement therapy (see Jacques E Rossouw et al, “Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women’s Health Initiative Randomized Controlled Trial” (2002) 288:3 *Journal of the American Medical Association* 321). In addition, the off-label promotion of the arthritis drug valdecoxib (Bextra), the epilepsy drug gabapentin (Neurontin), and the schizophrenia drug olanzapine (Zyprexa) resulted in criminal prosecutions, fines and settlements of hundreds of millions of dollars, and a record-setting settlement of US\$2.3 billion in the case of valdecoxib (see Gardiner Harris, “Pfizer Pays \$2.3 Billion to Settle Marketing Case”, *The New York Times* (2 September 2009), online: The New York Times <www.nytimes.com>).

³¹ See Wiktorowicz et al, *supra* note 24 at 165. Françoise Baylis has pointed out, for example, how pre-market clinical trials routinely exclude pregnant women, who subsequently receive prescription medication without sufficient evidence base (see Françoise Baylis, “Pregnant Women Deserve Better” (2010) 464:7299 *Nature* 689; Françoise Baylis & Chris Kaposy, “Wanted: Inclusive Guidelines for Research Involving Pregnant Women” (2010) 32:5 *Journal of Obstetrics and Gynaecology Canada* 473). The authors

There remains a surprising lack of research, publicly funded or otherwise, on the long-term safety and effectiveness of post-market drugs, despite the fact that regulators, policy-makers, health care providers, and consumers need this information to make well-informed decisions.³² A related problem is that clinical trials conducted for market authorization rarely investigate whether the drug is actually more effective than other alternative treatments already on the market.³³ Additional post-market studies on both long-term safety and efficacy and comparative effectiveness are therefore an essential supplement to pre-market clinical trials;³⁴ drug regulatory reforms should include a more explicit requirement for such studies.³⁵ Unfortunately, in Canada, inferior drugs simply tend to remain on the market unless a product is found to be unsafe; inferiority to existing products in itself is typically insufficient to ground market withdrawal.

Other important limitations relate to the design, conduct, and analysis of clinical trials. Sponsoring pharmaceutical companies are responsible for funding the majority of clinical trials, but various studies have shown that industry-sponsored research is more likely to be biased and yield positive outcomes than research with alternate sources of sponsorship.³⁶ Various

recommend more systematic requirements for research involving pregnant women, but this could certainly also extend to the post-market phase.

³² See Lorraine E Ferris & Trudo Lemmens, “Governance of Conflicts of Interest in Post-marketing Surveillance Research and the Canadian Drug Effectiveness Network” (2010) 4:2 *Open Medicine* E123 at E123.

³³ Another related problem worth mentioning is that the evidence required at the point of drug regulation and approval (occurring at the federal level) is different from that required at the point of public funding (at the provincial level)—this is referred to by Flood and Dyke as the “data divide”. In particular, they argue that the evidence of minimal efficacy generated for the purposes of regulatory approval does cast light on important questions around relative effectiveness or cost-effectiveness of drugs—information that is critical to making informed funding and treatment decisions (Colleen M Flood & Patrick Dyke, “The Data Divide: Managing the Misalignment in Canada’s Evidentiary Requirements for Drug Regulation and Funding” (2012) 45:2 *UBC L Rev* 283 at 300).

³⁴ See Gliklich & Mack, *supra* note 30 at 94.

³⁵ In other countries, regulatory agencies appear to intervene more firmly in this context. For example, in India, the Intellectual Property Appellate Board recently revoked a patent held by the pharmaceutical company Roche because of the drug’s unproven superiority to other products already on the market (see Kaustubh Kulkarni & Ben Hirschler, “India Revokes Roche Patent in New Blow for Big Pharma”, *Reuters* (2 November 2012) online: Reuters International <in.reuters.com>).

³⁶ According to Lexchin, biases may be introduced through a variety of measures, including “the choice of comparator agents, multiple publication of positive trials and non-publication of negative trials, reinterpreting data submitted to regulatory agencies, discordance between results and conclusions, conflict-of-interest leading to more positive

reasons can account for this trend, but there is sufficient evidence that carefully crafted research design, choices made in the context of statistical analyses, and exclusion of negative findings or over-inclusion of positive findings contribute to this phenomenon.³⁷

conclusions, ghostwriting and the use of ‘seeding’ trials” (Joel Lexchin, “Those Who Have the Gold Make the Evidence: How the Pharmaceutical Industry Biases the Outcomes of Clinical Trials of Medications” (2012) 18:2 *Science and Engineering Ethics* 247 at 247 [Lexchin, “Those Who Have the Gold”]). For an empirical study of the phenomenon, see also Andreas Lundh et al, “Industry Sponsorship and Research Outcome (Review)” (2012) 12 *Cochrane Database of Systematic Reviews*, Art No MR000033.

³⁷ There are a multitude of examples of pharmaceutical companies intentionally withholding and misrepresenting the results of unfavourable clinical trials in order to advance drug sales. Two high-profile examples involved the blockbuster drugs Paxil and Celebrex. In 2004, the State Attorney General of New York launched a fraud lawsuit against GlaxoSmithKline (GSK) for concealing clinical trial data about the safety and efficacy of Paxil. The suit alleged that GSK had conducted at least five studies on the use of Paxil in children and adolescents, but only published and disseminated one of the studies (suppressing the negative results of the other four studies) (see Press Release, “Major Pharmaceutical Firm Concealed Drug Information” (2 June 2004), online: New York State Office of the Attorney General <www.ag.ny.gov>). See also the detailed analysis of the Paxil studies in Jon N Jureidini, Leemon B McHenry & Peter R Mansfield, “Clinical Trials and Drug Promotion: Selective Reporting of Study 329” (2008) 20:1/2 *International Journal of Risk & Safety in Medicine* 73.

Pfizer has similarly been implicated for, among other things, its promotion of Celebrex: results of a 1999 clinical trial found that elderly patients taking Celebrex were at a much higher risk of suffering heart problems than patients taking a placebo. However, Pfizer chose not to publish the study and it was not submitted to the FDA until June of 2001 (see Alex Berenson & Gardiner Harris, “Pfizer Says 1999 Trials Revealed Risks With Celebrex”, *The New York Times* (1 February 2005), online: *New York Times* <www.nytimes.com>).

Pharmaceutical companies may also use their influence to try to suppress the publication of negative research results produced by independent researchers. For example, Nissen reports that GlaxoSmithKline attempted to stop the publication of their meta-analysis that showed that the diabetes drug Avandia was associated with a significantly increased risk of myocardial infarction (Steven E Nissen, “Setting the RECORD Straight” (2010) 303:12 *Journal of the American Medical Association* 1194).

A host of other products have been associated with equally problematic practices, including Oxycontin, Neurontin, Zyprexa, Fen-Phen, Prempro, Prepulsid, Depakote, Actimmune, Avandia, and Risperdal (see e.g. David Evans, “Big Pharma’s Crime Spree”, *Bloomberg Markets* (December 2009) 73, online: Canadian Health Coalition <healthcoalition.ca>; Donald W Light, ed, *The Risks of Prescription Drugs* (New York: Columbia University Press, 2010); Healy, *supra* note 2; Moynihan & Cassels, *supra* note 2; Young, *supra* note 2). See also the report by the public interest organization Public Citizen: Sammy Almashat et al, “Rapidly Increasing Criminal and Civil Monetary Penalties Against the Pharmaceutical Industry: 1991 to 2010” (2010), online: Public Citizen <www.citizen.org>.

II. Specific Challenges in Post-Market Surveillance

Health Canada itself admits that once a drug is approved, “as long as the drug causes no adverse reactions or the manufacturer does not need to make changes to the drug, it may never be subject to review by Health Canada again.”³⁸ Yet the drug manufacturer is in charge of collecting and forwarding adverse events to the regulator and therefore plays a key role in determining whether changes are “needed”. It has no financial interests in diligently pursuing the proactive verification of the safety and efficacy profile of an already marketed drug. It is therefore more accurate to state that as long as no *evidence* is being collected and forwarded by the manufacturer to Health Canada, a drug will rarely be reviewed again. Moreover, even a totally inferior drug can remain perpetually on the market as long as no strong evidence of serious side effects is reported.

Although, as we have emphasized, the current drug regulatory system focuses on pre-market activities, there are a number of obligations that manufacturers are required to adhere to once their drug enters the market. These include informing Health Canada of any reported serious adverse drug reactions (ADRs) to their product; complying with advertising restrictions set out in the *Food and Drugs Act* and regulations; updating safety information pertaining to their products; maintaining the quality of their drug to the appropriate standard; and applying for further authorization from Health Canada for significant changes to their product.³⁹

Unfortunately, Health Canada has only a limited ability to ensure continued compliance with regulations once a drug enters the market.⁴⁰ Health Canada traditionally appeared to lack the power to compel manufacturers to conduct new efficacy or safety studies or studies on therapeutic effectiveness once a drug product hits the market.⁴¹ Although drug manufacturers are encouraged to conduct post-market studies and to comply with post-market commitments, the current evidence suggests that they often fail to do so and that the regulatory agencies do not suffi-

³⁸ Health Canada, “Brief History of Drug Regulation”, *supra* note 7.

³⁹ See Health Canada, *Guidance Document: Submission of Pharmacogenomic Information* (2008), online: Health Canada <www.hc-sc.gc.ca>.

⁴⁰ Some of the few measures available are inspecting manufacturing compliance and removing a drug from the market for safety reasons (*ibid.*).

⁴¹ Health Canada believes it lacks the regulatory authority to explicitly require post-market studies as a condition for further sales of a pharmaceutical product (see Mary E Wiktorowicz et al, “Keeping an Eye on Prescription Drugs, Keeping Canadians Safe: Active Monitoring Systems for Drug Safety and Effectiveness in Canada and Internationally” ((Health Council of Canada, November 2010) at 4–5, online: Government of Canada <publications.gc.ca> [Wiktorowicz et al, “Health Council Paper”]).

ciently monitor and enforce post-market commitments.⁴² As such, there is a need for ongoing assessment of pharmaceutical industry compliance with post-market commitments and for appropriate sanctions for a failure to meet these commitments.⁴³ Since 1998, Health Canada has offered a special type of authorization, a Notice of Compliance with conditions (NOC/c), which allows the sponsor to market a drug in Canada on the condition that they undertake additional studies to confirm the clinical benefit of the product.⁴⁴ The NOC/c policy allows for earlier market access to potentially life-saving drugs, while the conditions tied to the authorization enable Health Canada to monitor the drug through enhanced post-market surveillance. Yet there are questions about Health Canada's control of the fulfillment of these conditions. In 2003, the original policy was modified following complaints that it was not being consistently applied and that there was a greater need to disseminate materials to accompany products that have been issued a NOC/c.⁴⁵ Joel Lexchin suggests there continues to be little oversight for drugs once they are approved under the NOC/c policy.⁴⁶

Other jurisdictions have strengthened more significantly the power of regulatory agencies to impose post-market studies under regular approval procedures. In the US, for example, the *Food and Drug Administration Amendments Act of 2007* expanded the FDA's authority to require manufacturers to conduct post-market studies (including clinical trials and observational studies) after market approval if new safety information

⁴² See Ferris & Lemmens, *supra* note 32 at E123.

⁴³ As recommended in a recent Health Council of Canada discussion paper, "[a]ny fines that are imposed for failure to complete Phase IV trials must be significant enough to achieve their objective; fines that are too small will not have any value" (Wiktorowicz et al, "Health Council Paper", *supra* note 41 at 41). Unfortunately, Health Canada has received significant criticism in recent years for its lack of enforcement activities. Of particular concern is the fact that the drug approval system is largely funded by the pharmaceutical industry through a user-fee system. Through these financial contributions, the industry has gained significant influence within the drug regulatory system and uses this influence to request a disproportionate distribution of funding towards fast drug approval, rather than long-term safety monitoring (see generally Tracey Epps, "Regulation of Health Care Professionals" in Downie, Caulfield & Flood, *supra* note 2 at 100).

⁴⁴ Health Canada, *Guidance Document: Notice of Compliance with conditions (NOC/c)*, (2011), online: Health Canada <www.hc-sc.gc.ca>.

⁴⁵ See Joel Lexchin, "Notice of Compliance with Conditions: A Policy in Limbo" (2007) 2:4 *Healthcare Policy* 114 at 116.

⁴⁶ *Ibid.* See also Wiktorowicz et al, "Health Council Paper", *supra* note 41 at 12 (discussing examples of cases in which Health Canada appears to have dropped the ball in terms of a follow-up after expedited approval).

comes to light.⁴⁷ The FDA can mandate that these studies be completed on a definite timetable. Following the passage of new “pharmacovigilance” legislation by the European Union in 2010, European regulatory authorities now also have the authority to require manufacturers to conduct post-market studies within the framework of a “Risk Management Plan”. Regulatory authorities may mandate “both safety and efficacy studies ... and the obligation may be imposed at the time of authorisation, or [after approval] if an important safety concern emerges.”⁴⁸

Fortunately, the federal government finally appears to be ready to take concrete steps toward enhancing regulatory oversight during the post-market phase. In December 2013, it tabled new legislation, Bill C-17 (Vanessa’s Law)⁴⁹, that includes provisions granting Health Canada the authority to compel drug companies to compile information, conduct new tests or studies, and monitor the use of drug products after market entry. An important complement to these amendments is a significant increase in penalties for violations of the *Food and Drugs Act* and its associated regulations: while the current maximum fine is \$5,000, the new maximum on indictment is \$5 million per day that the contravention is continued.⁵⁰ Moreover, where a person “knowingly or recklessly causes a serious risk of injury to human health,”⁵¹ there is no maximum fine set out, giving the court the discretion to impose even more substantial fines.

Overall, the expansion of Health Canada’s authority during the post-market phase provided for in Bill C-17, including the ability to impose further testing, represents an important step forward in strengthening the integrity of the drug regulatory system, particularly when backed by the threat of much more substantial penalty provisions. The bill undoubtedly represents an improvement over the status quo. Yet there are a number of important omissions in the legislation. As Herder and colleagues also point out, the bill does nothing to improve the transparency of clinical trials or Health Canada’s decision-making process around drug

⁴⁷ See the discussion in Barbara J Evans, “Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era” (2010) 85:2 *Notre Dame L Rev* 419.

⁴⁸ Patrick Waller, “Getting to Grips with the New European Union Pharmacovigilance Legislation” (2011) 20 *Pharmacoepidemiology and Drug Safety* 544 at 545.

⁴⁹ Bill C-17, *An Act to Amend the Food and Drugs Act*, 2nd Sess, 41st Parl, 2013.

⁵⁰ *Ibid.*, ss 21.31, 21.32, 31.2. Where an offence is committed or continued over multiple days, the maximum fine is multiplied by the number of days, significantly increasing the potential upper limit of the penalty. The maximum fines for a summary conviction are increased to \$250,000 for a first offence and \$500,000 for subsequent offences.

⁵¹ *Ibid.*, s 31.4.

approval⁵²; the central importance of such transparency provisions is discussed in more detail below. Further, the ultimate success of these provisions will depend on Health Canada having both the resources and political will to police and enforce the new provisions. Bill C-17 commenced second reading in April 2014 and will hopefully be passed later in 2014.

A. Adverse Drug Reaction Reporting

In Canada, the most common means of monitoring the ongoing safety and effectiveness of pharmaceuticals is through voluntary reporting of (actual or suspected) ADRs by health professionals and consumers. According to Health Canada, “[t]hese individual reports may be the only source of information concerning previously undetected [ADRs] or changes in product safety and effectiveness profiles.”⁵³ Although pharmaceutical manufacturers are required to report ADRs they become aware of to Health Canada, physicians—who are on the front lines in encountering ADRs in patients and therefore in a better position to gather this information—only need to submit ADR reports on a voluntary basis. Reporting is “therefore conditional on doctors having the time and inclination to do the additional paperwork.”⁵⁴

Mandatory physician reporting of ADRs is one measure that had been suggested to strengthen post-market surveillance.⁵⁵ Unfortunately, physician groups are resistant to mandatory reporting because the requirement would be time and labour intensive. Moreover, trying to enforce such a requirement would likely be very complex and time consuming for regulatory authorities. At the very least, physicians would want to be compensated for that time. Indeed, even in the absence of mandated reporting, simply remunerating physicians to report ADRs could provide a sufficient incentive to substantially increase the amount and quality of reports received. In addition, the expanded use of electronic medical records has been suggested as an important means of improving the quality and

⁵² Matthew Herder et al, “Regulating Prescription Drugs for Patient Safety: Does Bill C-17 Go Far Enough?” (2014) 186:8 Canadian Medical Association Journal E287.

⁵³ Health Canada, “Adverse Reaction Information”, *supra* note 27.

⁵⁴ Lauren Vogel & Tomek Sysak, “Physicians Should Be Paid to Report Adverse Drug Reactions, Experts Say” (2012) 184:8 Canadian Medical Association Journal E409.

⁵⁵ At a minimum, some commentators suggest that “Canada should follow New Zealand’s lead and require doctors to report all instances in which one of their patients suffer[s] an adverse effect from the use of a drug or a combination of drugs” (*ibid*).

quantity of ADR reports⁵⁶—and one that could streamline the reporting process and reduce the time commitment required of physicians.

Any measures to increase ADR reporting need to be coupled with improvements in the systems for collecting, storing, and analyzing ADR data;⁵⁷ the problem is not simply a lack of data, but a failure to structure data in an interpretable manner. Presently, the data collected by Health Canada’s adverse drug reaction reporting tool, MedEffect, is sporadic and often incomplete. Moreover, the MedEffect tool itself has been described as “poorly structured” and as compiling information that is “often uninterpretable”.⁵⁸ Many physicians are sceptical of the value of simply collecting more data since it is unclear how Health Canada uses the information. One way Health Canada could counter this is through being more open about how ADR reports inform the post-surveillance process. Health Canada should also receive more explicit powers to impose more stringent and independent ADR reporting requirements as part of the approval process.

Finally, it is worth mentioning here that privately developed databases are being developed, partly in response to the limited adverse event data collection of governments.⁵⁹ An interesting initiative to improve both the reporting of adverse events and the availability of the resulting data is the website RxISK.org. The website is described as the first free website (that is, not sponsored by the pharmaceutical industry or by advertising) to provide a means to easily report side effects to assist in individual patient care and to help other patients by “identifying problems and possible solutions earlier than is currently happening.”⁶⁰ RxISK.org is funded by selling subscriptions to the anonymous, aggregated data collected through the site. The initial basis for the RxISK adverse events database is cur-

⁵⁶ See Standing Senate Committee on Social Affairs, Science and Technology, *Prescription Pharmaceuticals in Canada: Post-Approval Monitoring of Safety and Effectiveness* (March 2013) at 10, online: Parliament of Canada <www.parl.gc.ca> [*Prescription Pharmaceuticals*].

⁵⁷ Members of the medical community have argued that the process for making an ADR report should be easier and should incorporate sufficient detail to draw conclusions on cause and effect (*ibid.*). A common way of recording data should also be established (see “Health Council Paper”, *supra* note 41 at 40).

⁵⁸ For example, “clinically important information, such as the time between a patient starting a drug and experiencing an adverse effect, must be dumped in ‘free text’ entry fields with a jumble of other information” (see Vogel & Sysak, *supra* note 54 at E409).

⁵⁹ See Shannon Gibson, *Direct-to-Consumer Advertising in the Digital Age: The Impact of the Internet and Social Media in the Promotion of Prescription Drugs in Canada* (LLM Thesis, University of Toronto, 2012) at 71 [unpublished, archived online at University of Toronto <tSPACE.library.utoronto.ca>].

⁶⁰ RxISK, “About Us”, online: RxISK <wp.rxisk.org>.

rent data supplied by the US FDA, with new adverse events data to be contributed by patients from around the world—this information is made anonymous and added to the database in “real time”.⁶¹ As another example, AdverseEvents, Inc. (AEI)⁶² also uses data taken from the FDA to create a database on side effects associated with FDA-approved prescription medications.⁶³ Users can pay to gain access to detailed information, such as the relationships between adverse events and patient demographics or prescription regimens, or outcomes such as hospitalization or death. These tools can be used to track potential trends and problems in the pharmaceutical industry.

The success of both RxISK and AEI depend in particular on consumers to directly report ADRs to these databases. Given the reluctance of many physicians to be burdened with the requirement to increase ADR reporting, consumers themselves will likely play an increasingly important role in reporting ADRs. Many consumers already share their experiences with drugs through online patient communities and would likely be eager to participate in initiatives like RxISK and AEI. While these online resources are certainly not a replacement for government-run reporting systems and rigorous scientific studies, they could nonetheless play an important role in raising warning flags about potentially serious ADRs earlier than might otherwise be possible.⁶⁴

B. Issues Around Off-Label Prescribing

As in many countries, off-label prescribing (that is, prescribing for uses for which drugs have not been officially approved) is legal in Canada—based largely on the premise that regulators lack the authority to control the practice of medicine.⁶⁵ Many physicians are in fact unaware that they

⁶¹ *Ibid.*

⁶² See AdverseEvents, “About AdverseEvents”, online: AdverseEvents <www.adverseevents.com>.

⁶³ Users can search the database for specific drugs to find the percentage of respondents that reported a specific adverse effect or the percentage that found a drug to be ineffective. According to their press material, AEI has created a unique set of online tools that is optimized to provide unparalleled access to adverse event information on over four thousand drugs, in an easy to understand and navigate format (AdverseEvents, “AdverseEvents Launches Innovative Comparative Drug Side Effect Reporting System at Health 2.0 Conference”, online: AdverseEvents <www.adverseevents.com>).

⁶⁴ See Gibson, *supra* note 59 at 73.

⁶⁵ However, it is worth noting that Health Canada prohibits the promotion of off-label use by the drug manufacturer. Specifically, section 9(1) of the *Food and Drugs Act* prohibits false, misleading or deceptive advertising. According to Health Canada, messages discussing off-label use of a drug product could be considered a contravention of section 9(1) (Health Canada, *Regulation of Health Products Advertising in Canada: Overview*

are prescribing drugs for off-label use.⁶⁶ Given the complexity of medical practice, as Patrick O'Malley argues, “it would be an enormous task to support labeling for every possible potential use.”⁶⁷ A certain amount of off-label prescribing can arguably therefore be acceptable, to allow physicians some flexibility in offering therapeutic options. Off-label prescribing can contribute to innovation in clinical practice, “particularly when approved treatments have failed[;] [i]t offers patients and physicians earlier access to potentially valuable medications” based on emerging evidence; and it may even provide “the only available treatments for ‘orphan’ conditions.”⁶⁸ However, as Joseph Emmerich, Nathalie Dumarcet, and Annie Lorence rightly emphasize, “such prescriptions must remain the exception to the rule and should be scrutinized and controlled by regulatory agencies using well-defined frameworks.”⁶⁹ To the extent that off-label prescription is acceptable, it has to be integrated in a framework that promotes evidence gathering.

Pharmaceutical companies are responsible for submitting the necessary safety and efficacy data to Health Canada to support the use of a drug for a specific indication. Additional indications may be added to a drug's label through a supplemental new drug submission. Generating this data requires substantial resources and financial risk.⁷⁰ Where a

for *Physicians* (2011), online: Health Canada <www.hc-sc.gc.ca>. Although in the US the FDA also prohibits the promotion of off-label prescribing, a recent federal appeals court decision “threw out the conviction of a sales representative who sold a drug for uses not approved by the [FDA] [on the grounds that] the ban on off-label marketing violated the representative's freedom of speech” (Katie Thomas, “Ruling Is Victory for Drug Companies in Promoting Medicine for Other Uses”, *The New York Times* (3 December 2012), online: The New York Times <www.nytimes.com>). This case creates concerns about the enforcement of restrictions on off-label prescription promotion, at least in the US. However, the right to freedom of expression is construed much more broadly in the US legal system than in Canada, so it is highly unlikely that a Canadian court would reach the same conclusion.

⁶⁶ “[S]ome off-label prescribing may be driven by doctors' mistaken belief that certain drugs are actually approved ... for such use.” In a 2009 survey of “1,200 psychiatrists and primary care doctors ... [t]he average doctor was wrong about the FDA approval status of 45 percent of the drugs he or she was asked about.” In the study, doctors were asked “to identify whether 14 common drugs were approved by the FDA for treatment of various illnesses” (Monifa Thomas, “Many Docs Off Mark on Off-Label Scripts”, *Chicago Sun-Times* (23 August 2009) 11A).

⁶⁷ Patrick G O'Malley, “What Does Off-Label Prescribing Really Mean?” (2012) 172:10 *Archives of Internal Medicine* 759 at 759.

⁶⁸ Randall S Stafford, “Regulating Off-Label Drug Use: Rethinking the Role of the FDA” (2008) 358:14 *New Eng J Med* 1427 at 1427.

⁶⁹ “France's New Framework for Regulating Off-Label Drug Use” (2012) 367:14 *New Eng J Med* 1279 at 1280.

⁷⁰ See O'Malley, *supra* note 67.

brand-name drug is already widely used off-label, manufacturers have little incentive to conduct costly clinical trials to support a new indication, especially since such trials could potentially yield non-supportive evidence.⁷¹ Randall Stafford warns that off-label prescribing “undermines the incentives for manufacturers to perform rigorous studies.”⁷² Many of the serious controversies in the last couple of years relate to the subtle and not so subtle promotion by industry of off-label prescription.⁷³

Drug labels provide information about the identified benefits and risks of drug products to help guide physicians and patients in drug treatment decisions. By disregarding the drug’s labelling, off-label prescribing “undercuts expectations that drug safety and efficacy have been fully evaluated [and] may discourage evidence-based practice.”⁷⁴ A 2012 study revealed that around 11 per cent of prescription drugs in Canada are prescribed for off-label use, and of these, 79 per cent lacked strong scientific evidence for the off-label use.⁷⁵ A similar study conducted in the US in 2006 found that 21 per cent of prescriptions were for off-label uses, and of that number, 73 per cent had “little or no scientific support”.⁷⁶

It is difficult to judge the scope or severity of the risk presented by off-label prescribing without knowing the corresponding clinical outcomes. Off-label prescribing is just one aspect of the broader issue of inappropriate use of medications.⁷⁷ The prevalence of off-label prescribing reflects the fact that there is inadequate monitoring of the use of medications during the post-market phase, particularly with regard to whether medica-

⁷¹ See Stafford, *supra* note 68.

⁷² *Ibid* at 1427–28. Stafford further states that off-label prescribing “subtly encourages [drug companies] to game the system by seeking approval for secondary indications for which clinical trials are less complicated and less expensive” (*ibid*).

⁷³ See e.g. Adriane Fugh-Berman & Douglas Melnick, “Off-Label Promotion, On-Target Sales” (2008) 5:10 PLoS Medicine 1432.

⁷⁴ Stafford, *supra* note 68 at 1427–28.

⁷⁵ Off-label use was highest for central nervous system drugs (26.3 per cent), including anticonvulsants (66.6 per cent), antipsychotics (43.8 per cent), and antidepressants (33.4 per cent) (see Tewodros Eguale et al, “Drug, Patient, and Physician Characteristics Associated with Off-Label Prescribing in Primary Care” (2012) 172:10 Archives of Internal Medicine 781).

⁷⁶ David C Radley, Stan N Finkelstein & Randall S Stafford, “Off-Label Prescribing Among Office-Based Physicians” (2006) 166 Archives of Internal Medicine 1021 at 1024. Note that one difference between this American study and the Canadian Eguale study (*supra* note 75) that may account for the higher reported prevalence of off-label prescribing in the former is that it included prescribing to children, whereas the Canadian study did not.

⁷⁷ As stated by O’Malley, “off-label use may actually be only a very crude marker of inappropriate use” (*supra* note 67 at 759).

tions are being prescribed appropriately. Therefore, reform efforts need to focus on moving toward better measurement and assessment of drug use based on clinical outcomes and on explicit and stringent requirements to conduct post-market clinical research to obtain reliable evidence of the effects of drugs in real-world settings.⁷⁸

Effective monitoring of off-label drug use requires the co-operation of the medical and scientific communities to identify and collect information about emerging off-label uses. Physician buy-in, in particular, would be crucial to implementing successful systems for the monitoring of off-label use since such systems would likely rely on physicians to share information about side effects and patient outcomes observed during clinical practice. However, as with mandatory ADR reporting, physician groups would likely be resistant to any increased monitoring obligations because the requirements could potentially be time and labour intensive. Both Lexchin and O'Malley note that the movement toward electronic health records would be an important development in improving our ability to effectively track both labelling indication and patient outcomes more systematically;⁷⁹ electronic health records may thus facilitate the collection of this information without requiring a significant reporting burden on physicians.

An example of a new regulatory initiative to control off-label use is France's recently launched "Temporary Recommendations for Use" (TRU) mechanism, which provides for temporary supervision of the prescribing of drugs for indications for which they are not yet approved. The TRU process establishes an observation window of up to three years to "assess the benefits and risks of a marketed drug for an unlicensed indication and to collect scientific information to ensure its safe use."⁸⁰ One potential drawback in the design of the TRU process is that pharmaceutical firms are given the responsibility for controlling off-label prescribing: "they must monitor prescriptions' adherence to marketing authorizations and must not market their drugs for unlicensed indications."⁸¹ As has been

⁷⁸ In particular, O'Malley advocates "an expanded comparative effectiveness research agenda [that focuses on] ways to more accurately link and monitor use with indication and disease identification with efficacious interventions" (*ibid* at 759–60).

⁷⁹ Comments by Joel Lexchin in Kate Lunau, "Off-Label Drugs Are Off the Charts in Canada", *Macleans's* (29 May 2012), online: *Macleans's* <www2.macleans.ca>; O'Malley, *supra* note 67.

⁸⁰ Emmerich, Dumarcet & Lorence, *supra* note 69 at 1280. Several factors must be considered and carefully balanced by an expert committee before a TRU can be issued: (1) the quality of the scientific evidence; (2) the drug's safety profile; (3) the prognosis associated with the given disease; and (4) the frequency of the disease's occurrence.

⁸¹ *Ibid.*

demonstrated with the significant bias that arises in industry-controlled clinical trials, it is questionable whether the pharmaceutical industry should be given the responsibility for monitoring off-label prescribing, since they tend to benefit from the practice. While the success of the TRU approach has yet to be proven, it nonetheless represents a possible means to encourage the development of new uses for marketed drugs while still monitoring the benefit-risk ratios for new indications.

C. Improving Information Sharing with Patients and Consumers

The goal of improved post-market surveillance is to ameliorate patient and consumer protection—not only by strengthening the knowledge base of regulators and health care decision makers, but also by improving patient and consumer knowledge and understanding. They are the ultimate beneficiaries of the entire drug regulatory system. This is not unique to post-market surveillance. Since this paper focuses on how processes can be developed to create tools that underlie better knowledge production in the post-market phase, it exceeds the scope of this paper to discuss all the possible ways in which patients and consumers can be better informed or protected against misinformation. But it is worth emphasizing, briefly, the crucial role of improved consumer information in the context of the surveillance system itself.

We already indicated that the assessment of pharmaceutical product safety ought not to be a one-dimensional process based on a one-point-in-time assessment by the regulator of data submitted by industry. It is not a process where patients and consumers ought to be purely passive receivers of information. Not only should they be involved in the decision-making process surrounding their care, they should also play a role in feeding back essential information on pharmaceutical products for the benefit of other patients and consumers. For example, in the context of off-label prescribing, it is essential that they are fully informed of the limited information available on the safety and efficacy of a particular product (which has not been tested for their specific condition or for their specific patient population), so that they are alerted to the need to be particularly cautious, and are thereby empowered to identify possible problems faster. As noted above, patients are expected to play an increasingly important role in the context of ADR reporting, whether it is reporting for off-label prescribing or not. But in order to do so, patients and consumers have to be adequately informed in the first place.

There is a growing realization that good knowledge translation is essential in the context of health care. Yet experts have pointed out how the risk information about marketed products provided by regulatory agen-

cies often fails to reach busy health care providers.⁸² It is even less likely to adequately inform patients. For example, while Health Canada requires that the product monograph that accompanies approved pharmaceutical products also contain information in lay language, most patients are not aware that they can access this information on the regulator's website.⁸³ This exacerbates a more fundamental problem: the reliability and completeness of the information being transmitted, which is largely based on data produced by industry.

Clearly, improving post-market surveillance will require improving communication with patients and health care providers. Some interesting initiatives in this context are worth mentioning here briefly as examples of what can be done. In Canada, the Minister of Health announced in June 2013 a new "Plain Language Labelling" initiative to improve the basic information provided to patients when they receive pharmaceutical products.⁸⁴ Those who have been critical of the existing drug regulatory system, such as parliamentary member Terence Young, who has been actively pushing for better patient protection in response to the death of his daughter due to the drug product Prepulsid, have been arguing for years that the basic information provided to consumers in Canada at the time of purchase of pharmaceutical products was problematic, and less clear than in other countries such as the United States.⁸⁵ A coroner's inquest into the death of Vanessa Young recommended in 2001 that the information provided in the labelling of drug products should be improved.⁸⁶ The Plain Language Labelling initiative aims to make relevant information more accessible through standardization of forms, provision of a basic table of facts about the drug (a so-called "drug facts table"), and the use of accessible language. Interestingly, it also explicitly includes plans to promote feedback from consumers by introducing mandatory contact information that patients can use to report adverse reaction reporting. This laudable initiative thus recognizes the connection between communication of risk information and ongoing interaction between patients, health care providers, pharmaceutical producers, and the regulator.

⁸² See *Prescription Pharmaceuticals*, *supra* note 56 at 11. See also Lisa M Schwartz & Steven Woloshin, "Lost in Transmission: FDA Drug Information That Never Reaches Clinicians" (2009) 361:18 *New Eng J Med* 1717.

⁸³ See *Prescription Pharmaceuticals*, *supra* note 56 at 12.

⁸⁴ See Health Canada, News Release, "Harper Government Launches Plain Language Labelling Initiative to Improve Drug Safety for Canadians: Proposed Changes Will Make It Easier for Canadians to Read Drug Labels" (14 June 2013), online: Health Canada <www.hc-sc.gc.ca>.

⁸⁵ See e.g. Young, *supra* note 2 at 139.

⁸⁶ *Ibid* at 312–13 (a discussion of these recommendations and others regarding improved communications).

In the United States, the FDA already has more consumer-oriented communication tools at its disposal. This includes a “Black Box” warning system,⁸⁷ used to emphasize serious risks associated with specific products, and a system of “Medication Guides” to be handed out to consumers for specific pharmaceutical products when the FDA deems that “certain information is necessary to prevent serious adverse effects” or when specific instructions are important to ensure the effective use of a product.⁸⁸ Still, pharmaceutical policy experts Lisa Schwartz and colleagues argue that patients in the US are not sufficiently or accurately informed with the information they receive. In particular, they point out that there is little information about how well a product works, and that patients tend to be overwhelmed by a laundry list of side effects without clear emphasis on what they may most commonly experience. They have therefore recommended the introduction of a very basic “Drug Facts Box”, a single page with essential information on drug products. They have successfully tested this system in two randomized trials.⁸⁹ When implementing its new “Plain Language Labelling” system, Health Canada may take some lessons from these findings.

III. Tackling the Data Deficit

A. *The Need for Independent Research*

While communication is essential, its success depends on the reliability of the knowledge to be transmitted. Given the evidence that clinical trials conducted by industry for the purpose of approval of drug products are more likely to be biased and yield positive results, the same problems would likely arise in industry-sponsored post-market research.⁹⁰ The ideal

⁸⁷ A “Black Box” warning is a prominently displayed box that the FDA may require to be placed on the label of a pharmaceutical product with appropriate warning of specific problems, and “particularly those that may lead to death or serious injury” (21 CFR § 201.57(c) (2013)). For an analysis of the FDA’s use of Black Box warnings, see Judith E Beach et al, “Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs” (1998) 53:3 Food & Drug LJ 403.

⁸⁸ US Food and Drug Administration, “Medication Guides”, online: FDA <www.fda.gov/drugs>.

⁸⁹ Lisa M Schwartz, Steven Woloshin & H Gilbert Welch, “Using a Drug Facts Box to Communicate Drug Benefits and Harms: Two Randomized Trials” (2009) 150:8 *Annals of Internal Medicine* 516.

⁹⁰ Various studies have revealed “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” (Ferris & Lemmens, *supra* note 32 at E123–24). See also Lemmens, “Leopards”, *supra* note 2 at 653; Wayne A Ray

solution to this fundamental problem would be to remove industry control over the conduct of all clinical trials and improve government oversight of clinical trials.⁹¹ This need not rise to the level of state-run clinical trials centres;⁹² simply removing the direct relation between the clinical trials industry and the pharmaceutical companies would already be an important step forward in improving the quality of clinical trials. Some jurisdictions have already implemented a system of governmentally commissioned, publicly funded post-market studies. In New Zealand, for example, the Medicines and Medical Devices Safety Authority (Medsafe) oversees a limited number of post-market studies through its contracted research centre, the National Pharmacovigilance Centre at the University of Otago. As a matter of policy, Medsafe prefers to conduct the studies through its research centre rather than have the clinical trials industry involved. Moreover, the organization has no legal authority to request studies from drug sponsors.⁹³

& C Michael Stein, “Reform of Drug Regulation: Beyond an Independent Drug-Safety Board” (2006) 354:2 *New Eng J Med* 194.

⁹¹ See recommendation in Lemmens, “Leopards”, *supra* note 2 at 653 (see additional references there to others who have also made this recommendation). See also Jerome H Reichman, “The Eleventh Annual Honorable Helen Wilson Nies Memorial Lecture in Intellectual Property Law: Rethinking the Role of Clinical Trial Data in International Intellectual Property Law: The Case for a Public Goods Approach” (2009) 13:1 *Marq Intell Prop L Rev* 1 at 58–64; Marc A Rodwin, “Independent Clinical Trials to Test Drugs: The Neglected Reform” (2012) 6 *Saint Louis University Journal of Health Law & Policy* 113.

⁹² For more detailed discussions of the idea of independent clinical trials, see Reichman, *supra* note 91 at 58–64; Lexchin, “Those Who Have the Gold”, *supra* note 36 at 257–58; Rodwin, *supra* note 91.

⁹³ See “Health Council Paper”, *supra* note 41 at 30. The commissioning of independent clinical trials is categorically different from some other interesting initiatives, which aim to ensure more rigorous independent assessment of data. See, for example, the Yale University Open Data Access (YODA) Project, which enables industry sponsors to commission independent analyses of their clinical trials by two independent research teams, with strict conditions of full data access (including access to all patient-level clinical data) and full transparency and independent publication of the results (Yale School of Medicine, “Yale University Open Data Access (YODA) Project: A New Approach to Evaluation and Transparency”, online: Yale School of Medicine <medicine.yale.edu>. See also Harlan M Krumholz & Joseph S Ross, “A Model for Dissemination and Independent Analysis of Industry Data” (2011) 306:14 *Journal of the American Medical Association* 1593). Two independent research teams recently published the first independent analyses conducted through the YODA Project. The analyses were funded by the company Medtronic and focused on Medtronic’s recombinant human bone morphogenetic protein-2, an orthobiologic agent used to promote bone growth in spinal surgery. The research team analyzed all the publicly available and company held data, and also re-evaluated the published literature on the product. Not surprisingly, the teams concluded that the early publications of the product underreported adverse events and emphasized results favourable to the product. The product was deemed not to offer any efficacy advantage and was associated with increased risks, even if the product was still

The more drastic reform of fully removing the control over the conduct of clinical trials from the pharmaceutical producers is necessary, in our view. It is unlikely to happen anytime soon, however, considering the aversion of current governments toward firmer governmental oversight over industry practices and also, in Canada in particular, the recent significant reductions in the federal bureaucracy. Even if such a reform would not necessarily require a huge new bureaucracy, it would certainly require some higher level of governmental control and more active involvement of regulatory agencies in the organization of clinical trials. It is therefore worth mentioning one partially positive initiative in Canada in this area: the establishment by the federal government of the Drug Safety and Effectiveness Network (DSEN). This organization supports “independent and scientifically rigorous real-world studies on the safety and effectiveness of post-market drugs in Canada and will connect to the research being conducted through a virtual network of Canadian centres of excellence in postmarketing pharmaceutical research.”⁹⁴ The DSEN can be an important source of funding for independent post-market research on the safety and effectiveness of drugs after they enter the market—research that serves as an important supplement to mandatory ADR reports and any post-market studies conducted by industry.⁹⁵ Yet the DSEN has two important limitations: its budget pales in comparison to the marketing and clinical trials budgets of large pharmaceutical companies, and its independence is weakened by the fact that it is housed under the Canadian Institutes of Health Research (CIHR), which itself is now aggressively promoting close collaboration with industry, particularly in the organization and conduct of clinical trials. In the last couple of years, the CIHR has also appointed two pharmaceutical industry executives to its Governing Council, appointments that highlight the closer ties with industry and create a perception of lack of independence.⁹⁶ Considering the

seen as being a valuable treatment option in specific circumstances (see Mark C Simmonds et al, “Safety and Effectiveness of Recombinant Human Bone Morphogenetic Protein-2 for Spinal Fusion: A Meta-Analysis of Individual-Participant Data” (2013) 158:12 *Annals of Internal Medicine* 877; Rongwei Fu et al, “Effectiveness and Harms of Recombinant Human Bone Morphogenetic Protein-2 in Spine Fusion: A Systematic Review and Meta-Analysis” (2013) 158:12 *Annals of Internal Medicine* 890; Harlan M Krumholz et al, “A Historic Moment for Open Science: The Yale University Open Data Access Project and Medtronic” (2013) 158:12 *Annals of Internal Medicine* 910).

⁹⁴ Ferris & Lemmens, *supra* note 32 at E123.

⁹⁵ *Ibid* at E124.

⁹⁶ See Ann Silversides, “Appointment of Pfizer Executive to CIHR Stirs Controversy” (2009) 181:11 *Can Med Assoc J* E256; William Ghali, Claire Kendall & Anita Palepu, “Pharmaceutical Industry Representation on CIHR’s Governing Council” (2010) 1:1 *Open Medicine* E26; Steven Lewis, “Neoliberalism, Conflict of Interest, and the Governance of Health Research in Canada” (2010) 1:1 *Open Medicine* E28; Françoise Bay-

overwhelming evidence of problems with industry-controlled clinical trials, these developments are worrisome and undermine the potentially positive role the DSEN could play in establishing trust in the clinical trials system and promoting independent post-market research.

In a 2013 report on post-approval surveillance, the Canadian Standing Senate Committee on Social Affairs, Science and Technology acknowledged these concerns, which were raised both at its hearings on pharmaceutical regulation and in a memorandum we submitted to the Committee in the context of these proceedings. In response, the Senate Committee called for a further independent assessment of the DSEN's ability to work independently from CIHR and Health Canada⁹⁷ but it declined to make any specific recommendations about its reporting structure, noting that "CIHR is currently viewed by Canadians as a trustworthy and well-regarded organization."⁹⁸ In our view, the high public esteem of an organization is of little relevance to a relatively straightforward institutional conflict of interest analysis, but the Senate's prudent recommendation opens the door for further reflection on the DSEN's structure. The Senate Committee also recommended that the Minister of Health provide assurances of the DSEN's financial sustainability, and that a publicly accountable oversight mechanism be established that would regularly evaluate its activities.⁹⁹ Finally, the Senate Committee suggested that the DSEN ought to develop an active post-market surveillance program focusing on adverse drug reactions.¹⁰⁰ If implemented, those recommendations should strengthen the independence and public accountability of the DSEN and improve post-market surveillance in Canada. But clearly, much will depend on the financial means that are put at the disposal of the organization and the concrete implementation of measures to strengthen its independence from industry.

lis, "An Intractable Conflict of Interest", *The Mark News* (3 December 2009), online: The Mark News <pioneers.themarknews.com>. See also Canada, House of Commons, Standing Committee on Health, *Evidence*, 40th Parl, 2nd Sess, No 47 (30 November 2009); Canada, House of Commons, Standing Committee on Health, *Evidence*, 40th Parl, 2nd Sess, No 49 (7 December 2009).

⁹⁷ See *Prescription Pharmaceuticals*, *supra* note 56 at 20.

⁹⁸ *Ibid* at 19.

⁹⁹ *Ibid* at 20.

¹⁰⁰ *Ibid* at 21.

B. Promoting Transparency and Data Access

1. The Raison d'Être of Transparency

An essential component of improving the quality of clinical trials data is transparency, an issue that has received significant attention in recent years, particularly with respect to clinical trials data. Yet transparency is clearly a crucial condition for the improvement of all forms of data gathering, both pre- and post-market entry. Mandatory clinical trials registration, publication of research results, and increased access to clinical trials data and other relevant clinical data related to pharmaceuticals are now widely viewed as crucial means to prevent industry from manipulating and obfuscating unfavourable clinical trial results.

Greater transparency and access to data have been recommended more generally, and many of the examples discussed above deal with pre-market clinical trials data. Yet transparency is as, or perhaps even more, crucial for post-market studies. Drug companies often benefit from the scarcity of post-market research, since studies may reveal the inferiority of their drug to existing treatments, or reveal the inappropriateness of the drug for indications for which it is already widely prescribed off-label; drug companies may be equally motivated to hide unfavourable study results in the post-market phase. Since post-market research is essential for the ongoing evaluation of drug safety and efficacy, and for improving clinical guidance on both comparative effectiveness and off-label use, any expanded transparency and access to data requirements should be extended to all clinical trials no matter at what stage of the product lifecycle they occur.

As has been discussed elsewhere in detail, data transparency gained momentum in the wake of controversies that involved pharmaceutical companies hiding and misrepresenting data in the scientific literature and subsequently using misleading publications to promote off-label prescriptions.¹⁰¹ More recently, the driving force behind an invigorated debate over data access has been the issue of wasteful spending of public funding. In 2012, Peter Doshi, Tom Jefferson, and Chris Del Mar published a paper in which they laid out the failure of the company to produce solid data that could undergird the World Health Organization's and various public health agencies' recommendations to stockpile the drug Tamiflu as part of pandemic preparedness.¹⁰² In their review, they docu-

¹⁰¹ See the more detailed discussion in Lemmens & Telfer, *supra* note 2.

¹⁰² Peter Doshi, Tom Jefferson & Chris Del Mar, "The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience" (2012) 9:4 PLoS Medicine 1 [Doshi et al].

ment the hurdles put up by the drug's manufacturer, Roche, in their quest for access to the data allegedly supporting this recommendation, the remarkable lack of diligence by public health agencies, and the official agencies' blind confidence in data hidden behind corporate walls. Doshi and colleagues note that while "systematic reviews of published randomized clinical trials (RCTs) are considered the gold standard source of synthesized evidence for interventions, ... their conclusions are vulnerable to distortion when trial sponsors have strong interests that might benefit from suppressing or promoting selected data."¹⁰³ Supported by their report of the billions of dollars in waste associated with the unsubstantiated stockpiling of Tamiflu, a drug they argued was not more effective than aspirin for the treatment of influenza, Doshi and his colleagues argue that researchers need access to clinical study reports (standardized documents submitted to drug regulators that contain the most complete record of the planning, execution, and results of clinical trials) in order to conduct the most reliable evidence synthesis.¹⁰⁴

Unfortunately, both industry and regulators tend to treat clinical study reports as confidential documents, thereby preventing the data from being studied by independent researchers. For example, when Health Canada approves a drug, they only make available a Summary Basis of Decision, which explains the scientific and benefit-risk information that the department considered in making their approval decision.¹⁰⁵ According to Lexchin, with only this limited information base, it is "virtually impossible to independently assess the safety and efficacy of new products."¹⁰⁶

Beyond clinical study reports, providing access to raw clinical trials data would significantly reduce the incentive for industry to misrepresent data, since, as stated by Peter Götzsche, "it would be a risky affair when others can check the methods and calculations against the trial protocol

¹⁰³ *Ibid* at 2.

¹⁰⁴ Doshi et al show in the article how the claims of actual effectiveness of Tamiflu in reducing hospital admissions and complications from influenza are questionable. In particular, significant evidence has emerged that Roche, the manufacturer of Tamiflu, failed to disclose large amounts of data from the clinical trials on the drug, and continues to sidestep requests from Cochrane Collaboration researchers to make this data available for review (*ibid*).

¹⁰⁵ Lexchin notes that "[t]hese documents lack information about the study protocol, the baseline characteristics of trial participants, the number of participants who withdrew and reasons for their withdrawal, primary and secondary efficacy outcomes, and fatal and nonfatal serious ADRs, by treatment arm" (Joel Lexchin, "Harmony in Drug Regulation, But Who's Calling the Tune?: An Examination of Regulatory Harmonization in Health Canada" (2012) 42:1 *International Journal of Health Services* 119 at 129).

¹⁰⁶ *Ibid* at 129.

and the raw data.”¹⁰⁷ Other potential benefits of granting access to raw data include improving the efficiency of health research by allowing the use of existing data for new studies, rather than requiring patients and researchers to go through the expensive and time-consuming process of collecting new data; and making “meta-analyses of trials studying similar interventions and patient groups much more reliable than if based on published summary data.”¹⁰⁸ Some medical journals are already moving toward full access to the data as a publication requirement. For instance, in direct response to the Tamiflu controversy, the British Medical Journal announced in October 2012 that, as of January 2013, the journal will only publish studies where the sponsor commits to making the relevant anonymized patient level data available on reasonable request.¹⁰⁹

The importance of access to the EMA data—and, in particular, the way in which it allows public interest-oriented scientists to strengthen the reliability of pharmaceutical information already out there—is highlighted by a recent proposal by Peter Doshi and colleagues, which aims at “Restoring Invisible and Abandoned Trials (RIAT).”¹¹⁰ With this bold—one could also say provocative—RIAT concept, Doshi and colleagues want to help correct the scientific literature on a host of blockbuster drugs. As a result of data disclosure in the context of litigation in the United States, as well as data made accessible as part of EMA’s access to information policy, which we will discuss further,¹¹¹ they have obtained access to around 178,000 pages of previously confidential company research documents. Preliminary analysis of this data has revealed possible instances of failure to publish relevant data and misrepresentation of clinical trials data, issues that Doshi and colleagues identified in their proposal. They are pushing for a correction of the distorted scientific reports and for a publication of analyses of the unpublished trials, inviting the research funders (mostly pharmaceutical companies) and investigators involved in these trials to declare their interest in doing so within the next year. Failure to do so, they argue, should enable independent investigators to take up this task and to either correct distorted publications, or to publish new analyses of unpublished data. With this eminent proposal, the authors are putting the companies, which obviously defend the reliable scientific basis

¹⁰⁷ Peter C Göttsche, “Why We Need Easy Access to All Data from All Clinical Trials and How to Accomplish It” (2011) 12:249 *Trials* 1 at 6.

¹⁰⁸ *Ibid.*

¹⁰⁹ See Fiona Godlee, “Clinical Trial Data for All Drugs in Current Use” (2012) 345 *Brit Med J* 7.

¹¹⁰ Peter Doshi et al, “Restoring Invisible and Abandoned Trials: A Call for People to Publish the Findings” (2013) 346 *Brit Med J* f2865.

¹¹¹ See Subsection III-B-4, below.

of their products, between a rock and a hard place: ignoring their invitation opens up the door to public criticism by external researchers and retraction or serious correction of the research that has been used to promote their products. Accepting the invitation means a potential public admission of serious flaws in the representation of the safety and efficacy data on their products. Ignoring the invitation will thus be impossible, even if it can be expected that companies will try to use legal means to challenge the initiative. The public nature of the data and the support the proposal has already received by editors of two leading medical journals¹¹² bodes well for this initiative. The initiative and its strong support also highlight the crucial role of access to data for the scientific community.

2. The International Move Toward Data Access

Internationally, the debate seems no longer to be about whether trial registration and results reporting are needed, but whether and how fuller access to data, often including raw data, supporting submissions to regulatory agencies and publications can be ensured. Already in 2004, a Ministerial Summit organized in Mexico by the World Health Organization (WHO) called for the establishment of a clinical trials registry.¹¹³ The WHO responded swiftly by developing an international clinical trials registry platform and by promoting the development of regional registries.¹¹⁴ In the context of this global momentum toward trial registration, several countries implemented trial registration and results reporting obligations. In the United States, Congress introduced in 2007 various changes to the *FDA Amendments Act* that include strict trial registration and results reporting requirements, accompanied by significant financial penalties for non-compliance.¹¹⁵ The Pan American Health Organization provided significant support for the establishment of regional clinical trial registries in Brazil and Cuba.¹¹⁶ Other organizations contributed to the promotion

¹¹² See Elizabeth Loder et al, “Restoring the Integrity of the Clinical Trial Evidence Base” (2013) 346 *Brit Med J* f3601.

¹¹³ “The Mexico Statement on Health Research, Knowledge for Better Health: Strengthening Health Systems” (Joint statement from the Ministerial Summit on Health Research in Mexico City, 16–20 November 2004) at 126–28, online: WHO <www.who.int>; WHO, *Ministerial Summit on Health Research*, WHA58/2005/REC/1 (2005), 58th Sess, at 126, online: WHO <www.wpro.who.int>.

¹¹⁴ For a detailed overview of international and national initiatives related to transparency, with a particular focus on the Americas, see Karmela Krleža-Jerić et al, “Prospective Registration and Results Disclosure of Clinical Trials in the Americas: A Roadmap Toward Transparency” (2011) 30:1 *Pan American Journal of Public Health* 87.

¹¹⁵ *Food and Drug Administration Amendments Act of 2007*, Pub L No 110-85, § 801, 121 Stat 823 at 904–22 [*FDA Amendments Act*].

¹¹⁶ For more details, see Krleža-Jerić et al, *supra* note 114.

of trial registration and other transparency measures. In 2008, the World Medical Association included for the first time in its Declaration of Helsinki, which can be considered the most influential international research ethics standard, the requirement to prospectively register every clinical trial and to report the results of research.¹¹⁷ Around the same time, medical journal editors announced that prospective registration of clinical trials prior to recruiting human research subjects would henceforth be a condition of the subsequent publication of the results of studies.¹¹⁸ As mentioned above, some medical journals demand full access to the data as a publication requirement.¹¹⁹

3. Canada's Hesitant Steps Toward Transparency

While at the international level various steps have been taken, Canadian progress remains embarrassingly slow.¹²⁰ In Canada, both an Auditor General¹²¹ report and a report of the Standing Senate Committee on Social Affairs, Science and Technology¹²² have recommended in recent years that Health Canada improve the transparency of clinical trials data used in its decision-making process. Yet these recommendations have not resulted in an unambiguous and firm regulatory response. Trial registration and results reporting requirements have been introduced in the revised Tri-Council Policy Statement by the federal funding agencies in 2011.¹²³ However, the provisions remain vague and can only be enforced

¹¹⁷ World Medical Association, *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (Declaration, amended at the 64th WMA General Assembly, Fortaleza, Brazil in 2013) at 34–35, online: WMA <www.wma.net>.

¹¹⁸ For example, in 2005, the International Committee of Medical Journal Editors implemented a policy that requires all clinically directive trials to be registered in an approved clinical trials registry in order for the study results to be published in any of the member journals. An expanded definition of clinical trials requiring registration was subsequently adopted in 2007. See International Committee of Medical Journal Editors, “Frequently Asked Questions: Clinical Trials Registration”, online: IMCJE <www.icmje.org>.

¹¹⁹ See Godlee, *supra* note 109.

¹²⁰ See the detailed discussion in Lemmens & Telfer, *supra* note 2.

¹²¹ Auditor General of Canada, “Chapter 4: Regulating Pharmaceutical Drugs—Health Canada” in *Report of the Auditor General of Canada to the House of Commons* (Ottawa: Office of the Auditor General of Canada, 2011) at 12, online: OAG <www.oag-bvg.gc.ca>.

¹²² Senate, Standing Senate Committee on Social Affairs, Science and Technology, *Canada's Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines* (November 2012) (Chair: Kelvin K Ogilvie).

¹²³ Canadian Institutes of Health Research, Natural Sciences and Engineering Council of Canada & Social Sciences and Humanities Research Council of Canada, *Tri-Council*

through withdrawal of funding by the funding agencies. Most importantly, they only apply to research conducted in federally funded institutions and thus not to the majority of industry-controlled clinical trials used in the drug approval process. These trials are largely conducted by private contract research organizations, whose compliance with Canadian research ethics standards and good clinical practices is in several provinces being verified by private, commercial REBs.¹²⁴

Although Health Canada announced back in 2007 that it was looking into the development of trial registration and results reporting, no such regulatory requirement has yet been introduced. Most recently, in a rather ambiguous move, the federal Minister of Health announced the establishment of a Health Canada registry of clinical trials. However, it is clear from the announcement and subsequent discussions that the registry simply aims at providing information to potential research subjects on the type of trials that are ongoing in Canada and that have been the object of a clinical trials submission with the agency.¹²⁵ This initiative appears to do little to diminish the problem of hiding relevant clinical trials results and aims rather at the promotion of clinical trials per se. Pressure to take firm action to promote transparency increased in April 2014 in the wake of media reports about the problems with respect to access to important safety data of some popular approved drugs.¹²⁶ Health Canada's response—the publication of a “summary report” of data about the controversial acne pill Diane-35 (six months after it announced it would do so)—does little to reassure Canadians that we are really catching up with other countries.¹²⁷ Surprisingly, the recent proposal to improve Health Canada's post-marketing powers (Vanessa's Law),¹²⁸ which contains several

Policy Statement: Ethical Conduct for Research Involving Humans (2010), online: Government of Canada Panel on Research Ethics <ethics.gc.ca>.

¹²⁴ See Trudo Lemmens, “Federal Regulation of REBs Review of Clinical Trials: A Modest but Easy Step Towards an Accountable REB Review Structure in Canada” (2005) 13:2&3 *Health Law Review* 39.

¹²⁵ See Health Canada, “Update: Registration and Disclosure of Clinical Trial Information” (19 October 2012), online: Health Canada <www.hc-sc.gc.ca>. See also the commentaries in *Macleans's* magazine by numerous industry experts on this development: Julia Belluz, “Dear Leona Aglukkaq: Researchers Write the Health Minister on Clinical Trials”, *Macleans's* (30 October 2012), online: Maclean's <www2.macleans.ca>; Julia Belluz, “Why is Canada Such a Laggard on Clinical Trials Regulation?”, *Macleans's* (5 November 2012), online: Maclean's <www2.macleans.ca>.

¹²⁶ See Diana Zlomislic, “Health Canada Releases Summary Report of Controversial Drug Diane-35”, *Toronto Star* (9 April 2014), online: Toronto Star <www.thestar.com>.

¹²⁷ Health Canada, “Summary Safety Review: DIANE 35 (Cyproterone Acetate and Ethinyl Estradiol)—Venous Thromboembolism (Blood Clot)” (2014), online: Health Canada <www.hc-sc.gc.ca>.

¹²⁸ See discussion at 963–65, above.

interesting improvements to post-market surveillance, also does not currently contain any specific reference about clinical trials transparency.

4. The Saga of Pharmaceutical Data Transparency in Europe

It is not clear why Canada trails so far behind other countries with regard to transparency and why the government seems so reluctant to move forward. But some recent European developments may be revealing in that context. Europe, which used to take a similar approach to Canada, has taken major steps over the last four years to improve data transparency and is now facing strong opposition by industry.

The European Medicines Agency (EMA) was first pushed to change its data access policy in response to recommendations in the context of a pediatric cancer drug trial inquiry, in which the European Ombudsman criticized the EMA for not providing access to all relevant data and urged the agency to change course.¹²⁹ Criticism by leading health researchers of the Cochrane Collaboration, such as Peter Gøtzsche, Peter Doshi, and Tom Jefferson, who had sought access to data for independent meta-analyses,¹³⁰ also added to the pressure on the EMA. In response, the EMA introduced in 2010 a new policy on access to documents related to medicinal products for human and veterinary use.¹³¹ Rather than starting from the premise that that data is confidential and that researchers have to justify their requests to access the data, the EMA embraced a presumption of accessibility: companies had to justify their requests that specific data sets should not be disclosed. Under this new policy, the EMA has “released more than 1.9 million pages in response to such requests” for non-clinical and clinical data related to EMA-approved products.¹³²

Then, in November 2012, during a public consultation process focusing on the implementation of transparency measures for clinical trials data,¹³³ the EMA announced that it would introduce a prospective data re-

¹²⁹ European Ombudsman, *Decision of the European Ombudsman closing his inquiry into complaint 2560/2007/BEH against the European Medicines Agency* (Strasbourg: European Ombudsman, 2010) at paras 83, 88, online: European Ombudsman <www.ombudsman.europa.eu>.

¹³⁰ Gøtzsche, *supra* note 2 at 139–42.

¹³¹ European Medicines Agency, *Policy on Access to Documents (Related to Medicinal Products for Human and Veterinary Use)*: Policy 0043, EMA/110196/2006, online: EMA <www.ema.europa.eu>.

¹³² “Court Orders EU Medicines Agency to Withhold Clinical Trial Results”, *EurActiv* (2 May 2013), online: EurActiv <www.euractiv.com>.

¹³³ One of the authors (TL) participated in this process. See European Medicines Agency, Press Release, “Workshop on Access to Clinical-Trial Data and Transparency Kicks Off

lease policy in 2013.¹³⁴ This prospective data release policy would result in the public sharing of data related to EMA-approved drugs on a publicly accessible website even without explicit request. At the start of this November 2012 consultation meeting, the EMA executive director bluntly stated that the question was no longer “if” access to the data had to be provided, but “how”.¹³⁵

The EMA’s plans were clearly placing Europe ahead of other jurisdictions with respect to data transparency, but they met strong—albeit not very open—resistance from industry. The ongoing saga around the EMA’s data policy may be indicative of the larger political and economic battles that are now emerging over data access, and it is therefore worth mentioning here in more detail.

While industry organizations participated in consultation meetings on the new data release plans, presenting themselves as constructive partners willing to support at least the concept of transparency and data sharing,¹³⁶ they also helped to mount legal opposition. They first did so through supporting the legal offensive of two US-based pharmaceutical companies, AbbVie—a spin-off consisting of much of the former medicines division of Abbott—and InterMune. In the winter of 2013, these companies launched a procedure before the General Court of the European Union requesting the annulment of the EMA’s decision to grant access to clinical and non-clinical information related to their drugs Humira and Esbriet. The EMA had informed the companies that it would release the clinical trials reports related to these drugs to researchers, and for one of the drugs also to a competitor who had requested access under the 2011 policy.

The Federation of Pharmaceutical Industries and Associations and the Pharmaceutical Research and Manufacturers of America applied to obtain intervenor status in support of AbbVie, while the European Confederation of Pharmaceutical Entrepreneurs intervened on behalf of InterMune; the European Ombudsman and the British Medical Journal did the same in

Process Towards Proactive Publication of Data” (23 November 2012), online: EMA <www.ema.europa.eu>.

¹³⁴ European Medicines Agency, *Publication and Access to Clinical-Trial Data*: Policy 0070, EMA/240810/2013, online: EMA <www.ema.europa.eu>.

¹³⁵ European Medicines Agency, *Access to Clinical-Trial Data and Transparency: Workshop Report* (2012), online: EMA <www.ema.europa.eu>.

¹³⁶ See e.g. European Medicines Agency, *Overview of Comments Received on “HMA/EMA Guidance Document on the Identification of Commercially Confidential Information and Protection of Personal Data Within the Structure of the Marketing Authorisation (MA) Dossier: Release of Information After Granting of a Marketing Authorisation”* (2012) EMA/330149/2012, online: EMA <www.ema.europa.eu> [EMA, *Overview of Comments*].

support of the EMA.¹³⁷ The support of major trade organizations for the court challenge is particularly noteworthy in light of the troubling recent history of both companies with respect to misrepresentation of data. As Jim Murray reports,

[i]n May 2012, Abbott ... pleaded guilty to misbranding a medicine (Depakote) for dementia and schizophrenia [and] acknowledged ... that they had for years delayed disclosing the full results of trials showing the medicine was no better than a placebo. The total fines and penalties amounted to [US]\$1.5 billion.¹³⁸

InterMune, for its part, has been in trouble with US authorities for failing to make full and timely disclosure of clinical trial results. Very recently, the Chief Executive of InterMune was criminally convicted for dissemination of false and misleading information about a clinical trial.¹³⁹ In light of this, the industry's frequent expressions of support for improved data sharing and transparency¹⁴⁰ lose much of their credibility.

The companies' most prominent arguments against the data sharing policy were based on the allegedly confidential nature of various components of the clinical trial reports: access decisions would violate the access to information regulations of the European Council¹⁴¹ and the companies' fundamental right to protection of confidential information as guaranteed by the *Charter of Fundamental Rights of the European Union*¹⁴² and by

¹³⁷ *InterMune UK Ltd v European Medicines Agency*, Order of 25 April 2013, T-73/13 at para 19, online: Curia <curia.europa.eu> [*InterMune*]; *AbbVie Inc and AbbVie Ltd v European Medicines Agency*, Order of 25 April 2013, T-44/13 at para 27, online: Curia <curia.europa.eu> [*AbbVie (25 April)*].

¹³⁸ "Fighting for Transparency on Clinical Trials", *EuropeanVoice* (7 May 2013), online: EuropeanVoice <www.europeanvoice.com>.

¹³⁹ *Ibid.* See *United States v Harkonen*, 510 Fed Appx 633 (Cal 9th Cir Ct 2013).

¹⁴⁰ See the numerous expressions of support for transparency in EMA, *Overview of Comments*, *supra* note 136. See also Ronald L Krall & Frank Rockhold, "Trial Registration: Putting Principles into Practice", online comment in response to Karmela Krleža-Jeric et al, "Principles for International Registration of Protocol Information and Results from Human Trials of Health Related Interventions: Ottawa Statement (Part 1)" (2005) 330:7497 *Brit Med J* 956.

¹⁴¹ More specifically, EC, *Council Regulation (EC) 1049/2001 of 30 May 2001 regarding public access to European Parliament, Council and Commission documents*, [2001] OJ L 145/43, art 4. This article specifies when European institutions have to refuse access to specific documents, including when privacy rights are at stake (*ibid*, art 4(1)(b)), and when the protection of commercial interests, including intellectual property, will be undermined (*ibid*, art 4(2)). In the latter case, disclosure is still warranted if there is an overriding public interest. The EMA policy is based on this notion of public interest in disclosure.

¹⁴² EC, *Charter of Fundamental Rights of the European Union*, [2000] OJ C 364/1, arts 7, 8, 17.

the *European Convention on the Protection of Human Rights and Fundamental Freedoms*.¹⁴³ They also claimed that access would violate the EMA's TRIPS-based obligations to keep data submitted to the regulator confidential.¹⁴⁴

The companies also requested an interim suspension of the data access decision, awaiting the final outcome of the case. Under European law, such a suspension can be granted if there is a reasonable basis in fact and in law for the claim (and thus a reasonable chance of success) and if the regulatory decision is likely to create harms that would be irreparable and irrevocable. Lawyers for the EMA had reasonably argued that if the court would conclude in the end that the EMA's disclosure had violated the companies' rights, the court could order financial compensation for the harm suffered.¹⁴⁵ Surprisingly, the president of the General Court sided with the companies, ruling that there was a reasonable basis for the claim that the companies' fundamental right to the protection of private and family life would be violated, and that the fundamental rights nature of these interests would make it impossible to undo the harms done if the final decisions would favour the claimants.¹⁴⁶

The president's suspension of data access was a clear victory for industry. It immediately affected data access decisions by the EMA. The agency likely became concerned that any company faced with a data access decision would now challenge the decision in court and obtain an interim injunction. Industry's support of the legal challenges made this outcome more likely.

¹⁴³ *Convention for the Protection of Human Rights and Fundamental Freedoms*, 4 November 1950, 213 UNTS 221, art 8, Eur TS 5.

¹⁴⁴ For a discussion (and rejection) of the TRIPS argument in the context of data disclosure, see Lemmens & Telfer, *supra* note 2.

¹⁴⁵ *AbbVie (25 April)*, *supra* note 137 at para 51. See also *InterMune*, *supra* note 137 at para 40.

¹⁴⁶ *AbbVie (25 April)*, *supra* note 137 at para 52; *InterMune*, *supra* note 137 at para 41. The interim ruling based on a privacy-rights characterization of clinical trials data secrecy seems extraordinary in light of the case law from the European Court of Human Rights that supports exactly the opposite claim: that access to important health- and safety-related information is an essential component of, among others, the right to the protection of private and family life and the right to life. See the discussion of primarily European case law in Lemmens, "Pharmaceutical Knowledge Governance", *supra* note 2 at 166–72. For other discussions of the human rights dimensions of data access, see Aaron A Dhir, "Corporate Selective Reporting of Clinical Drug Trial Results as a Violation of the Right to Health" in Marcia H Rioux, Lee Ann Bassler & Melinda Jones, eds, *Critical Perspectives on Human Rights and Disability Law* (Leiden: Martinus Nijhoff, 2011) 341 at 356–64; Lemmens & Telfer, *supra* note 2 at 99–110.

But industry's victory was short-lived. The EMA appealed the decision to the European Court. In two prudent appeal decisions, the European Court's vice-president stuck to a careful narrow analysis of the legal arguments of the president's interim decision.¹⁴⁷ Without entering into a discussion of the reasonableness of the companies' claims and the nature of the rights at stake, he simply affirmed that even if companies would have a fundamental privacy right over clinical trials data, this type of privacy right would not be of such nature that disclosure would inevitably create irreparable harm. The companies would have to show that it would be impossible to calculate the level of financial harm they would suffer as a result of disclosure in order to have the potential harm qualified as irreparable.¹⁴⁸

This reversal of the suspension put the EMA again in the driver seat, particularly after one of the companies, AbbVie, withdrew its challenge of the data access decision related to Humira. While this legal battle was unfolding, the European Parliament also provided strong support for data transparency in Europe when it voted in favour of a new clinical trials regulation, which—with the amendments provided in the European Parliament—contains strict requirements for data access and reporting.¹⁴⁹

Nothing seemed to stand in the way of the EMA's further implementation of a more proactive data release policy. It therefore came as a major surprise when, in May 2014, the EMA distributed draft documents to participants of its Clinical Trials Data Policy Advisory group,¹⁵⁰ documents that appeared to significantly strengthen pharmaceutical companies' control over data and to make prospective data access a technical obstacle course. Scientists severely criticized, for example, the EMA's proposed prohibition on downloading data, which would require them to look at clinical trials reports, sometimes consisting of tens of thousands of pages, on screen and on a page-by-page basis. The "Terms of Use" and "Redaction Principles" also made it clear that companies would submit two different files to the EMA, one with the full data, and one redacted for public

¹⁴⁷ *European Medicines Agency v AbbVie Inc and AbbVie Ltd*, Order of 28 November 2013, C-389/13 P(R), online: Eur-Lex <eur-lex.europa.eu> [*AbbVie (28 November)*]; *Inter-Mune*, *supra* note 137. For a more detailed commentary on the developments in the cases, see Trudo Lemmens, "Access to Pharmaceutical Data, Not Data Secrecy, is an Essential Component of Human Rights" (8 April 2014), online: University of Toronto Faculty of Law Blog <www.law.utoronto.ca/blog>.

¹⁴⁸ *AbbVie (28 November)*, *supra* note 147 at para 46.

¹⁴⁹ EC, *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*, [2014] OJ L 158/1, art 81 (in particular).

¹⁵⁰ One of the authors (TL) is a member of this advisory group and received the draft documents in that capacity.

use,¹⁵¹ thus undermining the idea of full data sharing. Most troubling, however, are the potential legal implications of the request that researchers sign “Terms of Use” (TOU) and “Redaction Principles”, which appear to trap the signer into a particular interpretation of the law. By signing the TOU, a data user would “acknowledge that the *Information* is protected by copyright and proprietary rights ... and can be considered commercially valuable.”¹⁵² Brand name pharmaceutical companies increasingly insist that clinical trials data is protected by copyright and proprietary rights, and is considered confidential commercial information. But whether and to what extent data is protected by such rights remains hotly contested, and is not firmly established in law. Many have convincingly argued that this data is a public good¹⁵³ and that case law supports access to data on the basis of health-related human rights.¹⁵⁴ Remarkably, the EMA would now ask scientists to recognize these rights while it is still involved in litigation where the EMA has an interest in arguing for the most restrictive recognition of these rights.

Perhaps even more troublesome is that researchers would also contractually agree that they could be sued under UK law “in accordance with the provisions of the Contracts (Rights of Third Parties) Act 1999.”¹⁵⁵ As a result, pharmaceutical companies will be able to challenge researchers directly in court for violation of the EMA’s TOU. This puts them in a very comfortable legal position, particularly when this right to sue is connected with the recognition of proprietary rights, copyrights, the commercial and confidential nature of some information, and the severe technical restrictions on data use, which make good faith violations of the TOU more likely.

This could have a significant chilling effect. The mere risk or threat of litigation could seriously hamper open scientific debate. Researchers may think twice about publicly challenging a company’s interpretation and

¹⁵¹ European Medicines Agency, “Redaction Principles (Draft)” (5 May 2014), Appendix 1 [unpublished, on file with authors, “Redaction Principles”].

¹⁵² European Medicines Agency, “Terms of Use (Draft)” (5 May 2014) [unpublished, on file with authors, “TOU”]. One of the authors (TL) raised these concerns in a letter to EMA’s executive director, Guido Rasi. For a link to the letter, and a further discussion of the legal implications see Trudo Lemmens, “EMA’s Proposed Data Release Policy: Promoting Transparency or Expanding Pharma Control over Data?” (30 May 2014), online: PLoS Blogs: Speaking of Medicine <blogs.plos.org>.

¹⁵³ See Reichman, *supra* note 91.

¹⁵⁴ See *supra* note 36.

¹⁵⁵ “TOU”, *supra* note 152. The *Contracts (Rights of Third Parties) Act 1999* ((UK), c 31) aims at overcoming the common law doctrine of privity, and allows third parties to enforce contractual provisions—for example, if the contract contains a specific provision to that effect.

representation of data or correct the published record on the basis of EMA-held data, as is being undertaken in the context of the RIAT proposal.

This troubling development is not entirely surprising. Even if the transparency movement has had some major victories, including the adoption of transparency requirements in the European Clinical Trials Regulation, opposition has been mounting. Other regulatory initiatives may be used by industry to fight transparency. The European commission recently released a draft directive¹⁵⁶ aimed at streamlining and strengthening trade secret protection in Europe. The draft directive does not explicitly refer to clinical trials, but the European Federation of Pharmaceutical Industries and Associations (EFPIA) has already jumped enthusiastically at the occasion, hinting at the need to protect the “proprietary know-how” of drug development, including in the “clinical trials phase”.¹⁵⁷ In the context of ongoing and largely secret transatlantic trade negotiations between Europe and the United States and Canada, the pharmaceutical industry has also been lobbying to strengthen data and IP protection.¹⁵⁸

Could the same reasons be behind Canada’s apparent reluctance to move toward full transparency of data? We cannot know for sure. But it is clear that significant financial interests are at stake and that the pharmaceutical industry is mobilizing worldwide to counter the push by the scientific community and civil society to promote data transparency. It is interesting to note that a recent Canadian initiative to promote clinical trials in the country, involving closer collaboration between the CIHR, Health Canada, and Rx&D, does not contain any reference to transparency, but mentions in contrast the strengthening of IP rights in clinical trials as an explicit component of the new initiative.¹⁵⁹

¹⁵⁶ EC, Commission, *Proposal for a Directive of the European Parliament and of the Council on the Protection of Undisclosed Know-How and Business Information (Trade Secrets) Against Their Unlawful Acquisition, Use and Disclosure* (Brussels: EC, 2013).

¹⁵⁷ European Federation of Pharmaceutical Industries and Associations, News Release, “EFPIA Welcomes the Commission’s Proposal on the Protection of Undisclosed Know-How and Business Information (‘Trade Secrets’)” (28 November 2013), online: EFPIA <www.efpia.eu>.

¹⁵⁸ See e.g. Biotechnology Industry Organization, “Transatlantic Trade and Investment Partnership: Comments” (Docket No USTR-2013-0019), online: <www.bio.org>.

¹⁵⁹ Government of Canada, News Release, “Strengthening Clinical Trials: New Coordinating Centre to Help Attract Research Investment in Canada” (24 April 2014), online: Government of Canada <news.gc.ca>. See also Canada’s Research-Based Pharmaceutical Companies, Canadian Institutes of Health Research & Association of Canadian Academic Healthcare Organizations, *To Your Health and Prosperity: An Action Plan to*

Conclusion

At the pre-market phase, decreasing the deficit of reliable safety and efficacy data depends on measures to demystify industry practice in the conduct of clinical trials and to improve access to the resulting data, including making it available for systemic review by independent researchers. At the post-market phase, decreasing the deficit of data on real-world use of drugs requires ongoing studies on the long-term safety and efficacy of drugs, including on comparative efficacy and off-label use. Concurrently, improved ADR reporting by industry, physicians, and consumers, coupled with better systems for collecting, storing, and analyzing reported data, is critical for early detection of potential problems with drugs. Effective ADR reporting can signal the need for more research into the safety and efficacy of a drug and lead to faster response by regulators and the medical profession in placing limitations on, or in extreme cases suspending, the use of a drug product.

Despite the historical fixation on the pre-market phase of drug approval, post-market surveillance is becoming increasingly important in the evolving drug regulatory environment.¹⁶⁰ In particular, Health Canada has been working since 2005 on a progressive licensing framework¹⁶¹ that, among other things, would enhance regulatory oversight of the post-market phase and give the government authority to require drug manufacturers to conduct post-market studies and to submit the resulting data for review. The progressive licensing framework embraces what is referred to as the “life-cycle approach” to drug approval, referencing the fact

Help Attract More Clinical Trials to Canada (Ottawa: Association of Canadian Academic Healthcare Organizations, 2012), online: ACAHO <www.achho.org>.

¹⁶⁰ One jurisdiction that has already made the move toward greater emphasis on the post-market phase is Japan. In 2002, Japan reformed its *Pharmaceutical Affairs Law* to focus more attention on post-market duties (rather than on pre-market and manufacturing activities) in an effort to ensure safety and efficacy of medical products. In particular, Japan more closely regulates post-market activities through a focus on “precautionary phases and early intervention, as well as the reexamination/reevaluation periods to ensure the drug’s continuing safety and efficacy” (Vanessa Eng, “Drug Safety: It’s a Learning Process” (2009) 24:1 *St. John’s Journal of Legal Commentary* 159 at 188).

¹⁶¹ In 2005, Health Canada launched the Progressive Licensing Project to explore reform proposals for the entire federal drug licensing system, from early clinical trials to market authorization, and the monitoring of drugs once they are on the market (see Health Canada, “Progressive Licensing: Background”, online: Health Canada <www.hc-sc.gc.ca>). The project was initiated as an acknowledgement of the need for the system to evolve in response to a number of important medical and social trends. In particular, Health Canada pointed to changes in public expectation around, *inter alia*, growing demands for compassionate access to drugs, for early access to promising new therapies, and for greater patient autonomy in drug treatment decisions, including determining acceptable levels of risk (see Health Canada, “Life-Cycle Management”, online: Health Canada <www.hc-sc.gc.ca>; Lemmens & Bouchard, *supra* note 2 at 361–64).

that drug regulatory decisions are based not simply on pre-market evidence, but on the entire body of evidence that accumulates throughout the life cycle of the drug.¹⁶² As such, an important element of this model is “the initial and ongoing collection, evaluation, and communication about drug information throughout the product life-cycle.”¹⁶³ Although the progressive licensing framework offers a number of improvements to the Canadian drug regulatory system,¹⁶⁴ one limitation is that the framework still relies primarily on drug manufacturers to conduct post-market studies of their own products.¹⁶⁵ Concurrently, an important trend on the drug development side has been the growing emphasis on personalized medicines and drugs for niche markets—markets in which the problem of the lack of solid evidence on drug safety and efficacy becomes even more pronounced because of the inherently limited patient population. Drugs for niche markets, such as pharmacogenomic products,¹⁶⁶ drugs that treat ra-

¹⁶² The progressive licensing model recognizes that “knowledge about how a drug works, both positively and negatively, increases throughout th[e] life-cycle as more and more people are exposed to the drug” (Health Canada, *The Progressive Licensing Framework: Concept Paper for Discussion* (Ottawa: Health Canada, 2006) at 11).

¹⁶³ *Ibid* at 12. Interestingly, models similar to the life-cycle approach have also been suggested in the context of drug funding decisions under the title of “Coverage with Evidence Development” (CED). As summarized by Flood and Dyke, “[r]ather than demanding that evidence of effectiveness and cost-effectiveness be presented at the time of the listing decision, a new drug may be publicly funded on the condition that further evidence is developed about the relative effectiveness of the drug” (*supra* note 33 at 313). While making reimbursement conditional on expanded post-market evidence generation represents a step in the right direction, significant challenges remain with respect to the effective design and governance of CED initiatives (see e.g. Danielle Bishop & Joel Lexchin, “Politics and Its Intersection with Coverage with Evidence Development: A Qualitative Analysis from Expert Interviews” online: (2013) 13 BMC Health Services Research 88 <www.biomedcentral.com>).

¹⁶⁴ For a good discussion of the potential effects of the progressive licensing framework on post-market safety, see Ron A Bouchard & Monika Sawicka, “The Mud and The Blood and The Beer: Canada’s Progressive Licensing Framework for Drug Approval” (2009) 3:1 McGill JL & Health 49 at 66.

¹⁶⁵ See Ferris & Lemmens, *supra* note 32.

¹⁶⁶ Pharmacogenomics involves the development of pharmaceutical agents in combination with diagnostic tests that are able to provide information about the possible effectiveness and toxicity of a drug based on the genetic profile of individuals. Some new pharmacogenomic drugs have received rapid market approval on the basis of targeted clinical trials in genetically selected patient populations (see Shannon Gibson & Trudo Lemmens, “Niche Markets and Evidence Assessment in Transition: A Critical Review of Proposed Drug Reforms” (2014) 22:2 Medical L Rev 200 at 209–11). Proponents of the rapid approval of pharmacogenomic drugs claim that post-market research can clarify the safety and effectiveness of the drug and include testing the drug in other genetically selected populations. A case study by Raziee, Lemmens, and Kimmelman on the development of the pharmacogenomic cancer drug cetuximab raises some questions about the integration of biomarker evidence in drug development (Hamid Raziee, Trudo Lemmens & Jonathan Kimmelman, “Scientific Evidence and Targeted Phar-

re diseases, or breakthrough drugs for the treatment of life-threatening diseases are sometimes given special consideration during the drug approval process. While there is a case for being more flexible about the amount of data required to support the approval of these drugs, particularly when no other treatment is currently available,¹⁶⁷ the limited approval basis makes it even more critical to assess the benefits and risks of these drugs through the ongoing collection and analysis of data after they enter the market.¹⁶⁸ If such post-market studies are not properly conducted, the uncertainty regarding the safety and efficacy of the niche product is not effectively counterbalanced.

Ultimately, while there have been some promising new initiatives in various jurisdictions and at the international level to combat the data deficit that arises during both the pre- and post-market phases of drug development, Canada continues to lag on a number of fronts. Health Canada's lack of progress in mandating clinical trials registration, result reporting, and overall transparency of clinical trials data, in particular, has been disappointing. While the creation of the DSEN and the enhanced post-market commitments contemplated under the proposed progressive licensing framework offer some hope of restoring public confidence in the independence of the drug regulatory system, greater emphasis needs to be placed on insulating clinical research from the influence of the pharmaceutical industry at all stages of drug development.

macogenomics Drug Approval" (Draft Paper delivered at the conference "Using and Abusing Evidence in Science and Health Policy", Banff, Alberta, 1 June 2012) [unpublished]). The study suggests that a failure to validate molecular hypotheses early in drug development can result in inefficiencies in research and healthcare delivery and can evoke concerns about the equitable nature of more narrowly tailored drug development.

¹⁶⁷ See Health Canada, "Life-Cycle Management", *supra* note 161.

¹⁶⁸ *Ibid.*