Remarks Before the Senate Committee on Social Affairs, Science, and Technology
Study on Prescription Pharmaceuticals
May 17, 2012

Matthew Herder, BSc(hons), LLB, LLM, JSM
Assistant Professor, Faculties of Medicine and Law
Dalhousie University

Introduction

Thank you Chair and fellow Committee members for the privilege of appearing before you today.

My remarks focus on the absence of transparency in and around the clinical trials process in Canada. The practice right now—pushed for by the manufacturer, and accepted by the regulator—is to keep clinical trial designs and data secret, confidential, hidden from independent review.

There are many reasons why this lack of transparency is problematic. Most important, keeping clinical trial designs and results secret creates a risk of harm to Canadian patients and, in some cases, can actually lead to harm. These risks and harms are avoidable and, for that reason alone, greater openness in the regulatory system should be required. (1)

In the first part of my comments I will offer three additional reasons *why* the regulatory system must be more transparent than it presently is, and then in the second part of my remarks close with some comments about *what* specifically should be more transparent.

Part 1: *Why* Greater Transparency is Needed

Reason#1: Keeping Clinical Trials Secret Violates a Fundamental Principle of Research Ethics

Every pharmaceutical, biologic or medical device submitted to Health Canada for approval has been previously tested on humans.

Keeping the knowledge that those participants help generate secret, to quote a recent article published in the *New York Times*, is a "disservice to those who volunteer their bodies for clinical trials." (2) It "undermines the philanthropy of human participants." (3)

Treating the information generated through clinical trials as confidential information also violates a fundamental principle of research ethics, namely, that all research involving human participants must have an acceptable harm to benefit ratio.

In the case of clinical trials involving a drug, biologic, or medical device, the potential harms to human participants are significant. In contrast, the only potential benefit is the generation of new knowledge.

However, if we accept that in order to count as "new knowledge" a scientific finding must be reproducible, then the alleged benefit of participation becomes illusory. When conditions of secrecy are imposed upon the trial, a significant barrier to reproducibility is introduced. Therefore, the harm to benefit ratio must—in every case—be considered unacceptable.

Clinical trials that are not published and kept confidential between the manufacturer and Health Canada thus violate the ethical principle that all research must carry an acceptable harm to benefit ratio.

Reason#2: Shifts in Scientific Knowledge, Product Development, and Regulatory Standards Demand Enhanced Transparency

We are in the midst of tremendous upheaval in molecular biology, in how companies develop products, and how regulators assess their safety and efficacy. The scientific literature is flooded with exciting but largely unproven genetic and epigenetic findings. Companies are using this wealth of new but poorly understood information to develop so-called "targeted" or "personalized" therapies, if not upfront, then to rescue a failed product after the fact. (4)

Moreover, manufacturers, clinician-investigators, and patient groups are demanding greater regulatory flexibility around what evidence of safety and efficacy should suffice for market approval. Regulators are, in turn, increasingly receptive to "alternative trial designs" given the difficulties of conducting large clinical trials with small sub-populations or individuals afflicted with rare diseases.

Yet two recent studies suggest the evidence behind approved orphan medicines for cancers (5) and neurological conditions (6) depart, in troubling ways, from important experimental standards. The authors of one of those two studies summarized the implications of their findings as follows in the *Journal of the American Medicine Association (JAMA)*:

> The Food and Drug Administration's flexibility regarding clinical trial designs for orphan cancer drugs has meant that these drugs can be approved on a more expedited time frame, and this approach may have some advantages, for example, in life-threatening circumstances or where no other therapeutic options exist. But our study found that such flexibility can also lead to a worrisome lowering of trial design standards, including a higher rate of acceptance of unblinded or single-group studies and the use of surrogate end points to assess efficacy. […] Excessive willingness to lower trial standards for orphan drugs can lead to identifying benefits that are not real or missing risks that are. [emphasis added] (7)

In other words, the authors of this study show that the pressure upon regulators to both accelerate approvals and accommodate alternative research designs can carry significant safety and efficacy trade-offs.

The rapid growth of genetic and epigenetic information and the challenges involved in using that information to better understand and treat human disease (8-9) will test the capacity of regulatory science in profound ways.

Therefore, transparency must be a pre-condition to any regulatory changes that are made in the name of accelerating and/or better accommodating new submissions for targeted therapies.

Reason#3: Secrecy is Wasteful; Transparency Creates Opportunities for Innovation

Greater transparency in Health Canada's decision-making and the evidence that informs it, promises two kinds of innovation benefits.

First, making Health Canada's decisions transparent can reduce redundant research and development efforts. Companies can learn from each other's mistakes.

Second, making available data submitted to the regulator gives other manufacturers the opportunity to aggregate those findings with their own (10), and predict whether patients will respond well to other treatments under investigation. (11-12)

Some manufacturers may focus on the potential downside of making data openly accessible, suggesting that others will "free ride" on their efforts.

I have three responses to this free rider concern. First, the drop-off in production of new treatments in the pharmaceutical industry is well documented. In an effort to address the problem, some companies have begun to embrace more open and collaborative models of innovation. Opening up clinical trial data may therefore be seen as an opportunity by at least some members of the industry.

Second, other measures already in place, including patent rights, the *Patented Medicine Notice of Compliance Regulations*, and "data exclusivity" protection for innovative products under the *Food and Drug Regulations* reduce the amount of competitive harm that open access to clinical trial data may occasion.

Third, and most important, the primary goal of health research is *not* knowledge production at all costs. Rather, the primary goal is to create robust evidence that can enable policy-makers and health care providers to make better decisions about how to allocate limited health resources, how to advance care, and so forth. In short, "research transactions serve crucial social ends." (13) The social importance of creating a robust evidence base to inform health care decision-making should therefore trump free riding concerns.

Part 2: *What* Should Be Transparent

To paraphrase a recent article it is time for the debate to shift away from why greater transparency is needed "to the specifics of doing so." (3) The remainder of my remarks focus on those specifics.

Presently, Canada is less transparent than other jurisdictions in essentially every part of the pre-market approval process. (See **Table 1** below)

Clinical trial registration is not legally required in Canada. This requirement is instead contained in guidelines (the *Tri-Council Policy Statement*) that do not capture all research in Canada, and which suffer from a lack of detail, poor oversight and enforcement. (14)

Further, only a subset of Health Canada's decisions regarding applications for market approval is publicly disclosed, and no results database has been created to allow for independent data analysis.

Therefore, the following three elements of the pre-market regulatory process should be made more transparent.

First, all clinical trials, including Phase 1 as well as observational studies involving a diagnostic or therapeutic intervention (drug, biologic, or medical device) should be subject to mandatory registration. Clinical trial registration is not a panacea (15-17), but it can mitigate gaming of trial results by manufacturers (e.g. modifying clinical end points) and bring to light important gaps between the published and unpublished evidence. (18-20)

Second, all of Health Canada's decisions regarding applications for market authorization and the reasons behind them should be open to public scrutiny. That is, regardless of whether an application for market approval succeeds, fails, is abandoned, or withdrawn, that outcome and any assessment performed by Health Canada should be transparent. The European Medicines Agency currently discloses its "refusals," and the Food and Drug Administration in the Unites States is contemplating doing the same. (21-22) Health Canada should move forward with its own plans to do the same.

Third, Health Canada should be empowered to release "full data reports" accompanying applications for market authorization. There are technical solutions to any potential patient privacy concerns that this action might raise. Coupled with more transparency in Health Canada's decision-making, providing comprehensive access to clinical trial data, stripped of any personally identifying information, will enable manufacturers to learn from each other's missteps, aggregate data, and streamline product development.

In sum, each of these changes to the pre-market approval process is necessary; none is sufficient on its own. Clear authority should be built into the *Food and Drug Act* and/or its regulations in order to allow Health Canada to adopt these critical transparency measures.

	United States	Europe	Canada
Pre-Market Approval			
Clinical trial registration required by law (applies to all research)	YES	YES	NO
Public access to "basic results" database	YES	NO	NO
Public access to "full clinical reports"	NO	NO	NO
Agency Decision-Making			
Full information re: Advisory committee hearings	YES	NO	NO
Full disclosure of all positive decisions and reasoning synopsis	YES	YES	NO
Full disclosure of all negative decisions and reasoning synopsis	NO	YES	NO

Notes: (1) Only piecemeal information about Health Canada's advisory committees (e.g. membership; date of meetings) is available online; (2) only a subset of all drugs and medical devices approved for sale in Canada have been publicly disclosed to date by Health Canada.

References

1. Herder, M. Unlocking Health Canada's cache of trade secrets: mandatory disclosure of clinical trial results. *CMAJ* **184(2)**, 194 –199 (2012).

2. Doshi, P. & Jefferson, T. Drug Data Shouldn't Be Secret. *The New York Times* (2012).at http://www.nytimes.com/2012/04/11/opinion/drug-data-shouldnt-be-secret.html

3. Doshi, P., Jefferson, T. & Del Mar, C. The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. *PLoS Med* **9**, e1001201 (2012).

4. Carey K. Avastin loses breast cancer indication. *Nat Biotech* **30(1)**, 6 **(**2012).

5. Kesselheim, A. S., Myers, J. A. & Avorn, J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *JAMA* **305**, 2320–2326 (2011).

6. Mitsumoto, J., Dorsey, E. R., Beck, C. A., Kieburtz, K. & Griggs, R. C. Pivotal studies of orphan drugs approved for neurological diseases. *Ann. Neurol.* **66**, 184–190 (2009).

7. Kesselheim, A. S. & Avorn, J. Clinical Trials of Orphan Drugs for Cancer—Reply. *JAMA: The Journal of the American Medical Association* **306**, 1545 –1546 (2011).

8. Kolata, G. Study Says DNA's Power to Predict Illness Is Limited. *The New York Times* (2012).at http://www.nytimes.com/2012/04/03/health/research/dnas-power-to-predict-is-limited-study-finds.html

9. The Predictive Capacity of Personal Genome Sequencing. *Sci Transl Med* (2012).doi:10.1126/scitranslmed.3003380.

10. Eisenberg, R. S. The role of the FDA in innovation policy. *Mich. Telecomm. Tech. L. Rev.* **13**, 345–388 (2007).

11. Kent, D. M. *et al.* An independently derived and validated predictive model for selecting patients with myocardial infarction who are likely to benefit from tissue plasminogen activator compared with streptokinase. *Am. J. Med.* **113**, 104–111 (2002).

12. Selker, H. P. *et al.* Random treatment assignment using mathematical equipoise for comparative effectiveness trials. *Clin Transl Sci* **4**, 10–16 (2011).

13. London, A. J., Kimmelman, J. & Carlisle, B. Rethinking Research Ethics: The Case of Postmarketing Trials. *Science* **336**, 544 –545 (2012).

14. Downie, J. The Canadian Agency for the Oversight of Research Involving Humans: A Reform Proposal. *Accountability in Research* **13**, 75 –100 (2006).

15. Law, M. R., Kawasumi, Y. & Morgan, S. G. Despite Law, Fewer Than One In Eight Completed

Studies Of Drugs And Biologics Are Reported On Time On ClinicalTrials.gov. *Health Affairs* **30**, 2338 –2345 (2011).

16. Sekeres, M. *et al.* Poor Reporting of Scientific Leadership Information in Clinical Trial Registers. *PLoS ONE* **3**, e1610 (2008).

17. Viergever, R. F. & Ghersi, D. The quality of registration of clinical trials. *PLoS ONE* **6**, e14701 (2011).

18. Turner, E. H., Matthews, A. M., Linardatos, E., Tell, R. A. & Rosenthal, R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N. Engl. J. Med* **358**, 252–260 (2008).

19. Whittington, C. J. *et al.* Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* **363**, 1341–1345 (2004).

20. Rising, K., Bacchetti, P. & Bero, L. Reporting bias in drug trials submitted to the Food and Drug Administration: review of publication and presentation. *PLoS Med* **5**, e217; discussion e217 (2008).

21. Executive Summary - Draft Proposals for Public Comment. at http://www.fda.gov/AboutFDA/Transparency/PublicDisclosure/ExecutiveSummary/ucm210718.htm

22. Regulation (EC) No 726/2004, articles 13(3), 12(3), and 11.