

A BITTER PILL TO SWALLOW: CANADIAN DRUG REGULATION

by

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DALHOUSIE UNIVERSITY
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DEDICATION

This thesis is dedicated to my mother, Susan Taylor, who died May 13, 2007. It is largely through her love and wisdom that I have become the man I am today.

-and-

I would like to also thank Michelle Gregus for her invaluable contribution, in support and love throughout the difficult drafting process.

TABLE OF CONTENTS

LIST OF FIGURES	ix
ABSTRACT.....	x
ACKNOWLEDGMENTS	xi
CHAPTER 1: INTRODUCTION.....	1
Lessons Learned From the VIGOR Study and Vioxx.....	2
(a) The Vioxx Withdrawal	2
(b) The VIGOR Study.....	3
(c) Science and the Law in Regulatory Decision-Making	5
(d) Setting a Minimal Standard for Research	8
Research Question	11
CHAPTER 2: A BACKGROUND TO DRUG REGULATION IN CANADA.....	15
Introduction.....	15
A Brief History of Drug Regulation	15
(a) Early Drug Oversight in Europe.....	15
(b) The British Experience.....	17
(c) Early Canadian Regulation: A Focus on Quality	18
(d) Toward Regulating Safety and Efficacy	20
(e) The Arrival of Clinical Trials and Ethical Guidelines.....	22
(f) Present Policy Initiatives and the Future of Drug Regulation	24
Setting the Stage: The Law and Institutional Players in Drug Approval.....	26
(a) Law Overseeing Drug Regulation	27
(b) Defining a Drug.....	28
(c) Law and Supporting Materials Regulating Clinical Trials.....	29
(d) Institutional Actors.....	30
From Birth to Death: The Life-Cycle of a Prescription Drug	31
(a) Stage 1: Pre-Approval	31
(i) Discovery	31
(ii) Pre-Clinical Testing	32
(iii) Clinical Trials.....	34
(b) Stage 2: Approval.....	34
(i) New Drug Submission	34
(ii) Drug Identification Number and Notice of Compliance.....	36
(iii) Special Access and Priority Review	36
(c) Stage 3: Post-Approval Stage.....	37
(i) Drug Pricing	37
(ii) Drug Scheduling	38
(iii) Listing in Provincial Formularies	38
(iv) Monitoring Drug Safety at the Marketed Health Products Directorate	39
(v) Prescriptions and the Administration of Release	40
(vi) The Expiry of Patents and Generic Drugs.....	41
(vii) Disposal.....	42

Science and Law in the Regulatory Process	43
(a) Science in the Drug Life-Cycle	43
(i) Science in Pre-Approval	44
(ii) Science in Approval	44
(iii) Science in Post-Approval.....	45
(i) Law and Policy at Pre-Approval.....	46
(ii) Law and Policy at Approval.....	47
(iii) Law and Policy at Post-Approval	48
CHAPTER 3: REGULATING BIAS, SOUND SCIENCE AND THE CLINICAL TRIAL.....	50
Introduction.....	50
TeGenero (TGN-1412): A Costly Lesson in Clinical Research	50
Toward a Science of Experience and Good Experimental Design	53
(a) The Early Evolution of Experimental Medicine	53
(c) Tuskegee and the Limits of Unfettered Scientific Experimentation	56
(d) The Modern Clinical Trial.....	57
(e) Randomized Control Trials	59
(i) Randomization	60
(ii) Blinding.....	60
(iii) Controls.....	61
(iv) Measurable Variables or End Point Variables	62
(f) A Note on Hypothesis Testing and Valid Sampling.....	63
(g) A Note on Ethical Refinement of Research	65
(h) Sources of Research Bias	66
(i) Common Sources of Research Error.....	66
(j) Error in the Data used in the Approval Process	68
The Law and the Regulation of the Clinical Trial	70
(a) Statutory Authority to Legislate Clinical Trials	72
(b) The Food and Drug Regulations	73
(c) The Clinical Trial Application.....	74
(i) Investigator’s Brochure.....	75
(ii) Clinical Trial Attestation.....	75
(iii) The Protocol.....	76
(d) Good Clinical Practices.....	77
(e) Scientifically Sound and the Provision of a Protocol.....	77
(f) Study Protocol, Good Clinical Practices and the ICH Guidelines.....	79
(i) ICH Guidelines.....	79
(ii) Defining Good Clinical Practices in the ICH Guidelines	80
(iii) ICH Topic E8: General Considerations for Clinical Trials	81
(iv) ICH Topic E9: Appropriate Statistical Principles.....	82
(v) The Protocol under the ICH guidelines.....	83
(vi) The ICH Guidelines in Perspective.....	84
(g) Further Guidance from the Tri-Council Policy Statement (TCPS)?.....	85
(i) A Patient-Centred Perspective	85
(ii) Clinical Equipoise and Accurate Study Design	87

(iii) The TCPS and Administration of Trials	87
(h) The Assessment of Sound Scientific Methodologies	88
(i) Qualified Investigators	88
(ii) Health Canada	90
(iii) Research Ethics Boards.....	91
CHAPTER 4: AN IMPROPER BALANCING OF CONCERNS.....	94
Introduction.....	94
A Relative Standard of Safe: The Faustian Bargain in the Use of Any Drug	96
Balancing the Appropriate Concerns for Regulatory Oversight of New Drugs ...	99
Weakening Science by Over-Emphasizing Access.....	103
(a) Conceptualizing the Problems Underlying Access – A Drug Lag?	104
(b) Letting the Market Decide.....	107
(c) The Government’s Strategy: Equating Access with Speedy Approval.....	108
(i) The Therapeutic Access Strategy (TAS).....	110
(ii) Is there a Drug Lag in Canada?.....	117
(iii) Speed at the Expense of Safety?	118
(d) True Access for Patients.....	119
(i) ‘Necessary’ or Me-Too for New Drugs	120
Weakening Science by Emphasizing Innovation?	124
(a) Defining Innovation.....	125
(b) Patent Protections and the Incentives to Innovate?	127
(c) Commercialization, Innovation and the Degradation of Academic Science.....	133
(i) Commercialization of Research	133
(ii) Denigrating the Quality of Drug Research	136
(iii) Commercialization and the Denigration of Drug Research.....	138
CHAPTER 5: THE FUTURE DIRECTION OF DRUG REGULATION IN	
CANADA	143
Introduction.....	143
The Pull Towards a Life-Cycle Model	147
(a) Health Canada’s Blueprint for Renewal.....	147
(b) The Canadian Food and Consumer Safety Action Plan (CSAP)	151
(c) Progressive Licensing.....	153
Bill C-51 and the Progressive Licensing Model	155
Risk and the Life-Cycle Model	159
(a) Whither Risk-Benefit Analysis.....	161
(b) Cost-Benefit Analysis	162
(c) Risk-Benefit Assessment.....	164
(i) The Health Canada Decision-Making Framework (DMF)	165
(ii) Defining Risks.....	167
(iii) Uncertainty and Risk.....	172
(iv) Defining Benefits	174
(d) Good Risk-Benefit Analysis – Bad Risk-Benefit Analysis.....	177
Pharmacovigilance	181
(a) What is Pharmacovigilance?	183
(b) The Emergence of Pharmacovigilance.....	185

(c) Two Paths for Pharmacovigilence.....	188
(i) The EMEA and US-FDA Experiences with Pharmacovigilence.....	191
(ii) The United States Food and Drug Administration (US-FDA).....	193
Conclusion	197
(a) Taking the Measure of the Life-Cycle Model	197
(b) The Downside to Progressive Licensing.....	199
(c) General Statement	204
CHAPTER 6: CONCLUSION.....	206
Vioxx Revisited.....	207
Hitting the Right Balance.....	209
Whither the Regulator.....	211
BIBLIOGRAPHY	215

LIST OF FIGURES

Figure 1: The Progressive Licensing Model	154
Figure 2: The Health Canada Decision-Making Framework	167

ABSTRACT

This thesis assesses the current status of Canadian prescription drug regulation and the policy drivers that guide this process. This analysis is accomplished by first providing a general survey of the steps, law, and institutional players involved in the full life-cycle of a drug. Next the evolution of current clinical trials and the gaps that the present legal regime creates in the scientific standards employed in clinical research is reviewed. This is followed by a discussion of how commercialization (innovation) and speed of approval (market access) are slowly becoming the dominant policy drivers for the Canadian regime. Finally a discussion of the proposed Progressive Licensing model, and Bill C-51-*An Act to Amend the Food and Drug Act*, raises the concerns with a shift to a system largely based on risk assessment and post-market monitoring (pharmacovigilance).

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CHAPTER 1: INTRODUCTION

Our inexhaustible supply of fact has unexpectedly made everything true and false. While the power of expertise has obscured the causes of both success and failure.¹

As a society we place a lot of faith in science. In making decisions we rely on it to add weight to our choices, and to give them a layer of objective justification. Yet science is not truth or absolute; it is merely a tool to aid reasoning. One of its core principles is uncertainty, and the continuous need to check and modify the assumptions we draw from observation.² Like any tool it has its limits; when employed appropriately it is very useful, and when employed improperly, its utility to aid reasoning becomes questionable.

Too often, science is employed poorly when its outcomes have economic and political implications. Too often, observations can be manipulated to justify (predetermined) decision-making without maintaining validity. Under these circumstances, the value of science becomes negligible. In those situations where potential hazard flows from the decisions we make based on scientific observation, we must ensure that these observations do not shade into the meaningless.

¹J. R. Saul, *Voltaire's Bastards: The Dictatorship of Reason in the West* (New York: Vintage Books, 1992) at 175.

²See K. Popper, *The Logic of Scientific Discovery* (New York: Rutledge, 2004) [Popper].

Lessons Learned From the VIGOR Study and Vioxx

(a) The Vioxx Withdrawal

In 1999, Canada and the United States approved for sale the anti-inflammatory drug, Vioxx (Rofecoxib). It was heralded as a breakthrough in the treatment of arthritis, as the first in a new generation of drugs (COX-2 inhibitors) that targeted the physiological mechanism at the source of arthritic pain. It quickly became one of the most widely prescribed drugs in the world. Scarcely five years later in September 2004, Merck, the drug's manufacturer, announced the worldwide market withdrawal of Vioxx.

This withdrawal came after years of contradictory reports about the drug's safety.³ Not only had it been linked to increased intestinal bleeding, but also to the potential for increased heart failure. Several new studies had suggested that Vioxx increases the danger of cardiovascular complications.⁴ The FDA's own scientists speculated that it may have caused as many as 100,000 unexpected heart attacks in the United States alone.⁵ Yet despite these warnings, North American drug regulators were slow to act, arguing that the science was equivocal and that the benefit provided by COX-2 inhibitors far outweighed their risks.⁶

³P. Juni, L. Nartey, S. Reichenbach, R. Sterchi, P. A. Dieppe & M. Egger, "Risk of Cardiovascular Events and Rofecoxib: Cumulative Meta-Analysis" (2004) 364 *The Lancet* 2021 (PUBMED).

⁴*Ibid.*

⁵J. Lenzer, "FDA is Incapable of Protecting US Against Another Vioxx" (2004) 329 *BMJ* 1253 [Lenzer].

⁶H.A. Waxman, "The Lessons of Vioxx – Drug Safety and Sales" (2005) 352(25) *NEJM* 2576 [Lessons].

(b) The VIGOR Study

One of the largest studies with the greatest potential to shed light on the effects of long-term consumption of Vioxx was the Canadian-led VIGOR (Vioxx Gastrointestinal Outcomes Research) study. Sponsored directly by drug manufacturer Merck, it was a large, randomized trial designed to assess the incidence of gastrointestinal bleeding from two NSAIDs (non-selective non-steroidal anti-inflammatory drugs), Vioxx and Naproxen.⁷ The VIGOR study had the potential to be a very influential piece of research. With over 8076 patients at 301 different institutions in 22 countries, it represented large investments of time and resources by both researchers and drug manufacturers into the long-term consequences of taking Vioxx. The study's outcome would have massive potential to affect the prescribing behaviour of physicians and the overall safety perception of the product.

As the trial progressed, several expected cases of GI distress were observed, but surprising too was a significant increase in the incidence of heart attacks in the group taking Vioxx. When the researchers first published their data in the *New England Journal of Medicine* (NEJM), they focused their findings only on the GI data, downplaying any results suggesting Vioxx's relationship with increased risk of heart

⁷C. Bombardier, L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davis, R. Day, M. B. Ferraz, C. J. Hawke, M. C. Hochberg, T. K. Kvien, T. J. Schnitzer, "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis" (2001) 343(21) *NEJM* 1520 (PUBMED) [VIGOR Study].

attack.⁸ The logic of the researchers was that they had only an obligation to report those findings that were strictly within their original research protocol, regardless of the importance of this new safety data.⁹

When this omission became apparent in 2005, the NEJM editors chastised the VIGOR researchers for intentionally withholding adverse event data and other inaccuracies in their reporting of results.¹⁰ In 2006, the NEJM issued a harsher rebuke of the authors of the VIGOR study.¹¹ On the basis of newly released court documents, they asserted that at least two of the study authors knew of Vioxx-induced heart attacks and had knowingly withheld adverse event data at the request of Merck, going so far as to delete raw data submitted to the journal in support of the article. The NEJM editors suggested that, “taken together, these inaccuracies and deletions call into question the integrity of the data on adverse cardiovascular events in this article”.¹²

As the study’s underlying conclusions slowly became apparent, Merck directed its marketing representatives to “not initiate discussions on...the results of the VIGOR

⁸From their final data, the VIGOR researchers intentionally excluded three participants who had experienced heart attacks. According to their rationale, these adverse events were excluded because they occurred soon after the date set for end of the trial, even if observations continued. See G. D. Curfman, S. Morrissey & J. M. Drazen, “Expression of Concern Reaffirmed” (2006) 354(11) *NEJM* 1193 [Reaffirmed].

⁹C. Bombardier, L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davis, R. Day, M. B. Ferraz, C. J. Hawke, M. C. Hochberg, T. K. Kvien, T. J. Schnitzer, “Response to Expression of Concern Regarding VIGOR Study” (2006) 354(11) *NEJM* 1196 at 1198 [Response].

¹⁰G. D. Curfman, S. Morrissey & J. M. Drazen, “Expression of Concern: Bombardier et al. ‘Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis’” (2005) 353(26) *NEJM* 2813 [Concern].

¹¹*Reaffirmed, supra* note 8.

¹²*Ibid.*

study”.¹³ Worse, methods were developed to distort the results of the VIGOR study, as one author noted:

On the basis of purely theoretical reasoning, and in the absence of any evidence from randomized controlled trials, Merck proposed that the explanation for the observed differences in rates of myocardial infarction was the cardio-protective potential of the comparator drug used in VIGOR, naproxen.¹⁴

As a result, Vioxx continued to be widely prescribed even after dangers suggested by the VIGOR research were becoming known to researchers and industry.

(c) Science and the Law in Regulatory Decision-Making

Law and science often make poor bedfellows. Yet in most regulatory decisions involving risk, they walk hand in hand to form the underpinnings of decision-making. Science provides the empirical underpinning for inferential comparisons by weighing different options with systematic observation. Appropriately applied science should be hesitant to assert complete truth; it can be cautious and methodically slow in finding solutions to real-world problems, and hesitant in the universal conclusions it draws from limited observation.¹⁵ Law is a medium largely of human reasoning and experience designed to address the immediacy of competing concerns, making value judgments, and establishing authority¹⁶ to address broad problems in human affairs. Good science begins with observation and tests reasoning/hypotheses related to that observation.

¹³*Lessons, supra* note 6 at 2577.

¹⁴P. A. Dieppe, S. Ebrahim & P. Juni, “Lessons from the Withdrawal of Rofecoxib: Patients Would be Safer if Drug Companies Disclosed Adverse Events Before Licensing” (2004) 329 *BMJ* 867 [Dieppe].

¹⁵*Popper, supra* note 2.

¹⁶See A. Pecezenik, *Law and Philosophy Library 8: On Law and Reason* (New York, Springer: 2009).

Conventionally, law begins with reasoning (sometimes compassion) and uses logic (often doctrinal or jurisprudential analysis) to order observations. Neither is without bias or the potential for manipulation.

In the drug regulatory process, these two systems of knowledge work together to inform, change, and guide decisions relating to new drugs. A full perspective must take into account the most accurate scientific data on a drug's safety, and value judgments about the legal, political, and social impact of the new drug. All drug approvals are based on the interpretation of scientific data; the law has attempted to formulate its legal requirements based on accepted models of scientific inquiry, and these models and the proof generated for approval have in turn adapted to meet those criteria identified as most important by the law. Within this system, science informs legal and policy decisions; law, in turn, adapts and adjusts its perspective to respond to the implications of science. Science may then ask modified questions based upon these conventions established by law. The danger in this process is that science may too easily mould itself to meet the minimum needs established by law or policy, thereby distorting its veracity and limiting its ultimate utility.

Wherever regulatory decision-making rests on the interpretation of scientific evidence, it must employ science properly.¹⁷ If decision-making is to be based upon indices derived from scientific observation, the accuracy of those decisions rests largely on the accuracy inherent in our observations. In any regulatory system based on scientific

¹⁷This does not mean that regulatory decisions must rely only upon science; rather that in those cases where it employs science, it should be generated and considered using the best possible scientific norms.

norms, we must be ever vigilant that distortion or dilution of scientific observation does not lead to potential harm.

In the last decade, we have seen a push for increased speed in regulatory approval of new drugs, at the same time as an increase in the number of new products withdrawn for safety reasons.¹⁸ It is likely that many of the difficulties observed in the approval process stem from points at which law and science fail to function complementarily. When science is lacking, there is no rational basis for making meaningful conclusions about a drug's value; when law is not effectively used, gaps in applying safeguards arise, and only minimal scientific standards will be applied.

The decision to release potentially dangerous products for public consumption is never a simple task. How much risk to accept in return for benefit when dealing with a specific drug is never reducible to an empirical formula. It involves the assessment of competing concerns, and predictive judgments often based on unclear or ambiguous data. Science can never determine with certainty that a particular drug is absolutely safe. Instead it can only provide evidence that must be weighed by decision-makers. Yet, the drug approval process is often predicated upon the provision of greater certainty than can be gained from science. Placing a high premium on scientific observation, regulatory decisions regarding risk often require value judgments that are hardly objective or impartial. Instead they require projecting upon clinical data inferences and certainty that go far beyond what can actually be observed. In formulating inferences that go beyond

¹⁸J. Lexchin, "Drug Withdrawals from the Canadian Market for Safety Reasons, 1963-2004" (2005) 172(6) *CMAJ* 765 (PUBMED) [Lexchin Withdrawals].

what scientific observations can demonstrate, regulators and law-makers formulate mechanisms that have moral and ethical implications.

(d) Setting a Minimal Standard for Research

There is an assumption among the wider scientific community and the lay public that researchers will act conscientiously in generating and reporting research findings. It is assumed that the authors of a study submitted to the NEJM would be conscientious in reporting their research, ensuring that all available and relevant data are included in the study's results. The VIGOR study's authors argued that they had met their obligations by being strictly "in line with basic clinical principles".¹⁹ In the eyes of the authors, they had adhered to the minimum standards of study design and trial administration. Any inaccuracies that resulted from the following of this widely accepted methodology were not their fault or concern. The VIGOR study authors felt no larger ethical or legal obligation to report the potentially important adverse event data concerning Vioxx.

One might ask, where were regulators during this debate? Unfortunately, regulators do little to dispel the notion among the drug research community that they must meet only minimum standards. While there was mounting evidence that Vioxx was potentially dangerous, regulators did little to help clarify the debate by calling for research with definitive results. Instead, as one editorial in the *Canadian Medical Association Journal* (CMAJ) suggests:

¹⁹Response, *supra* note 9 at 1198.

[regulators] put their emphasis and resources into assessing drug benefits, not harms. The bar for approval is low...Pre-marketing approval trials are too small to flush out all of the risks of a drug. The built-in bias toward approving drugs without adequate assurance of their safety and with only a fragmentary and under-funded mechanism for post-approval surveillance based on physician reporting of isolated adverse events is a fundamental and (often literally) fatal flaw.²⁰

Regulators play a largely passive role, relying upon mostly industry sponsored and submitted research to form the core basis for their drug approval decisions. Yet, the majority of industry-sponsored research on which approval decisions will ultimately be based is far more likely to have favourable outcomes (3:1), or remain unpublished if unfavourable.²¹ A recent study found that in a survey of 324 large cardiovascular trials published in the leading peer review journals, those sponsored by industry were likely to report a positive result 90 per cent of the time, in contrast to 50 per cent for independent research.²²

The VIGOR study was hardly an isolated incident. Current research into the effects of drugs has come to be dominated by a strict adherence to established methodologies, research protocols, and reduced or weakened scientific standards, even as it is acknowledged that these practices may not be fully informative or approximate the

²⁰Canadian Medical Association, "Editorial: Vioxx - Lessons for Health Canada and the FDA" (2005) 172(1) *CMAJ* 5 at 5 [Vioxx Lessons].

²¹J. Lexchin, L. A. Bero, B. Djulbegovic & O. Clark, "Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review" (2003) 326 *BMJ* 1167 [Outcomes] and M. Bhadari et al., "Association Between Industry Funding and Statistically Significant Pro-industry Findings in Medical and Surgical Randomized Trials" (2004) 170(4) *CMAJ* 477 [Bhadari].

²²P. M. Ridker & J. Torres, "Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-for-Profit Organizations: 2000-2005" (2006) 295(19) *JAMA* 2270 (PUBMED).

most accurate science to back the ultimate safety and utility of a drug.²³ As one author has noted:

Researchers and research institutions operate within the narrow confines of the regulations and the landscape created by the regulations...[the result] is that researchers will allow regulations to set minimum standards for conduct.²⁴

When the health and safety of Canadians is based upon data generated by poor drug research, the erosion of science to suit commercial needs places their safety at risk. Allowing this erosion of drug research to proceed represents a “scandal in medical science that is at least the equivalent of any of the recent corporate scandals”.²⁵

There is a cautionary message here; all is not well in the world of prescription drug research and new drug approvals. The past decade has witnessed an increased percentage of new drugs pulled from the market after safety concerns came to light.²⁶ At the same time, we have seen regulatory emphasis shifting toward greater ties with industry²⁷ and a speedier approval process.²⁸ Increasingly, scholars are becoming critical of the Canadian drug approval process for being prone to errors due to reliance on poor safety data.²⁹ Other scholars have gone further, calling into question the very impartiality and validity of the scientific research upon which these decisions are based, hinting that

²³See J. Abramson, *Overdosed America* (New York: Harper Collins, 2004) [Overdosed].

²⁴M. E. Wiktorowicz, “Emergent Patterns in the Regulation of Pharmaceuticals: Institutions and Interests in the United States, Canada, Britain, and France” (2003) 28(4) *Journal of Health Politics, Policy and Law* 615 at 618 [Wiktorowicz].

²⁵*Overdosed*, *supra* note 23 at xiii.

²⁶*Lexchin Withdrawals*, *supra* note 18.

²⁷Government of Canada, *Canada’s Innovation Strategy* (Ottawa: Public Works and Government Services Canada, 2002), online: <<http://innovation.gc.ca/gol/innovation/site.nsf/en/in04113.html>> [Innovation].

²⁸*Lexchin Withdrawals*, *supra* note 18.

²⁹J. Lexchin, *Transparency in Drug Regulation Mirage or Oasis?* (Ottawa: Canadian Centre for Policy Alternatives, 2004), online: <<http://www.policyalternatives.ca/bookstore>> [Mirage or Oasis].

gaps created in the scientific process have allowed for the health of the general public to be put at risk.³⁰

Research Question

In the following thesis, I will investigate the legal and policy standards imposed on clinical research used in new drug approvals, and how potentially this has led to some science which is less than ideal. Underlying this thesis is an assertion that in those circumstances where science is used as a tool in regulatory decision-making, it must be employed correctly. If methodologies or sound scientific design are allowed to degrade as a result of low regulatory standards or poor policy, the research observations that flow from these studies become weak and their ability to demonstrate a drug's safety or utility become meaningless. It is my ultimate aim to demonstrate how poor standards of science are being permitted by present law and policy, and how this leads to inadequate research upon which to base regulatory decisions, which in turn puts the safety of the drug-consuming public at risk. To fully explore this problem, I will outline the present drug regime, describe deficiencies in the law, assess some of the dominant policy motivations driving law-makers and regulators, articulate difficulties that are common when integrating science and law, and postulate some solutions that might address these difficulties.

³⁰*Overdosed, supra* note 23 & J. Lexchin & D. W. Light, "Commercial Influence and the Content of Medical Journals" (2006) 332 *BMJ* 1444.

It was my original research intent to assess the approval decisions and quality of science employed by the Therapeutics Products Directorate (TPD) at Health Canada in the course of considering applications for new drug approvals. Unfortunately, analysis of this point in the drug life-cycle is hampered by limited and restricted access to industry data at Health Canada for external researchers. As a result, it was decided that a more useful approach would be to look further back in the process at that point where the science for approval decisions is generated. My focus has shifted to the law and policy governing the clinical trial process and the generation of research results that are ultimately used in approval decisions. It can be assumed that if the research which generates data used in the approval process is flawed, then the ultimate approval decisions may also be flawed.

In the first chapter, I will provide some background on the drug regulatory regime in Canada. I will first briefly outline the history of drug regulation in Canada. I will also identify many of the important institutional actors and laws which impact on this process. Next, I will describe a drug's legal life-cycle in detail, to serve as a backdrop for the assessment of issues raised. Finally, I will show how science, law, and policy are operating throughout this life-cycle to influence the outcome of regulatory decisions.

In the second chapter, I will look more closely at the law governing the clinical trial process. I will first describe the operation of the clinical trial process, and then survey some of the criticisms that have been raised regarding the veracity and methodology of modern drug research. I will next survey the law which impacts on

clinical trials, and identify the breadth and force of these various provisions. I will then demonstrate how this law places only the most cursory obligations on researchers to employ rigorous scientific methodology. Instead, emphasis is placed on the rational justification of a given methodology regardless of its scientific merit.

In the third chapter, I examine how misdirected policy considerations have led regulators away from the original policy objectives of ensuring that drugs are safe and effective. A legitimate drug regulatory system must account for safety, efficacy, innovation, and access. I will describe how increasingly, innovation and access are coming to dominate the policy behind new drug approvals to the potential detriment of safety and efficacy. I will then appraise the modern conceptualizations of innovation as economic value, and access as speeding up drug approvals. I will demonstrate how these conceptualizations have the potential to degrade the quality of science used in the development and approval of new pharmaceuticals.

I will next turn my attention to some of the emerging drivers of risk regulation and policy in Canada. There has been a shift toward increased use of post-market safety measures and the introduction of risk-benefit analysis as a standard for drug approvals. Embodied in the Progressive Licensing life-cycle model, these new trends have great promise but must be implemented in such a way that they do not detract from the overall safety of new drugs.

In my conclusion, I will try to identify some solutions that can help mend the cracks that have appeared in the regulatory process. It will consider the ethos that currently drives actors in the drug regime and ask whether we need to consider varying goals in the development, use, and justification of pharmaceuticals.

CHAPTER 2: A BACKGROUND TO DRUG REGULATION IN CANADA

Introduction

In the following chapter, I will provide a background to the present drug regulatory regime. This will include reviewing the development of drug regulation in Canada and abroad, several of the major institutional actors and their relationship to one another, the primary laws and statutes which regulate the system, the legal process influencing the development of a new drug, and how science, law, and policy overlap throughout this process.

A Brief History of Drug Regulation

The history of drug regulation in Canada and elsewhere has followed a very clear legal evolution. It begins with manufacturing standards and laws to ensure the quality and composition of products, progresses to include laws overseeing the general safety of these products for consumption, and finally pairs that safety with the effectiveness of products for intended or advertised uses. This evolution in the regulatory law, and widening concern for oversight in the consumption of these products, often occurs in parallel with public health disasters that produce massive public concern.

(a) Early Drug Oversight in Europe

The idea of controlling and testing what humans can or cannot consume to treat illness is a relatively new concept. In pre-classical times, as Erwin Ackernecht notes:

The causes of disease and the action of a drug were considered magic [so] there was little place for trial and error and even less for experiment to ascertain the effects of drugs.³¹

The dominant Western model for most of recorded history, flowing from Hippocrates (7th century B.C.) and Galen (2nd century A.D.), was that we should “treat the state of the sick individual [but] not the disease”³² by balancing the body’s humours. In this conception, treatments needed to be tested “through experience with different patients”.³³ A host of untested practices (bleedings, purges, and remedies) were applied in the hope that a patient would become better. Each medical practitioner largely relied upon his or her own judgment to develop a collection of treatments and medical techniques. This allowed for the dangerous bias that these treatments were “effective [and] gave credentials to large numbers of useless products, some of which were also toxic”.³⁴

A humeral conception of illness dominated medicine until the sixteenth century, when a collection of scientists in Europe, largely at the University of Paris, began to systematically appraise the value of existing medicines through clinical observations of outcomes. These reappraisals lead to the removal of some of the most extreme potions from the Paris 1758 edition of the *Codex Medicamentarius* including “hair, mummy, human blood, skull, placenta and urine”.³⁵ It was found that many long-held beliefs, common practices, and medicinal substances used in the treatment of illness in medieval

³¹E. H. Ackernecht, “A Short Survey of Drug Therapy to 1900” in J. B. Blake eds., *Safeguarding the Public: Historical Aspects of Medicine Drug Control*, (Baltimore: Johns Hopkins Press, 1970) at 53.

³²*Ibid.* at 51.

³³*Ibid.* at 55.

³⁴J. Avorn, *Powerful Medicines: The Benefits, Risks, and Cost of Prescription Drugs* (New York, Knopf, 2004) [Avorn].

³⁵A. Berman, “Drug Control in Nineteenth-Century France: Antecedents and Directions in Safeguarding the Public: Historical Aspects of Medicine Drug Control” in J. B. Blake ed., *Safeguarding the Public: Historical Aspects of Medicine Drug Control*, (Baltimore: Johns Hopkins Press, 1970) at 3 [Berman].

Europe had little value, and in some cases were even more hazardous for patients than the illnesses themselves.

This led some local governments in Europe to pass decrees determining who may provide medications and marking specific (often toxic) substances illegal.³⁶ Early legislation represented only a patchwork of disparate laws, which reflected the caprice of local governments and varied from region to region. Wider regulation of medications took the development of “two historical streams that came together only recently”³⁷ as Avorn notes:

The first was the political evolution that gave governments the authority to decide what products could be sold as medicines and how they could be promoted. The second was the scientific evolution that accorded experimental data priority over received wisdom.³⁸

Throughout the eighteenth and nineteenth centuries, as science pointed to the merits and perils of certain medicines, the sale of drugs slowly came to be legislated at the national level in continental Europe.

(b) The British Experience

Britain was slow to adopt drug regulation, remaining for an extended period a “stronghold of staunch laissez-faire philosophies”³⁹ where market forces determined which cures, potions, and elixirs were sold to treat ailments. In 1860, the poisoning of

³⁶See *Ibid.*

³⁷*Avorn, supra* note 34 at 42.

³⁸*Ibid.* at 42-43.

³⁹See E. W. Steib, “Drug Control in Britain, 1850-1914” in J. B. Blake ed., *Safeguarding the Public: Historical Aspects of Medicine Drug Control*, (Baltimore: Johns Hopkins Press, 1970) at 15 [Steib].

several hundred clients by a chemist who accidentally put arsenic in peppermint lozenges led to the passage of the *Bill for Preventing the Adulteration of Articles of Food and Drink*⁴⁰ by the British Parliament. The purpose of this regulation was to ensure the purity of a product, by requiring that it was “not adulterated with poisonous or unintended substances”.⁴¹ In 1872 further amendments were made that set more basic requirements overseeing the fabrication and sale of medications.⁴² However, these regulations remained voluntary and “left it up to local authorities whether or not to appoint inspectors or [conduct] analysis”.⁴³ It was not until 1875, under *The Sale of Food and Drugs Act*,⁴⁴ that inspections became mandatory.

(c) Early Canadian Regulation: A Focus on Quality

Canadian drug regulation had its “roots in English law and arose from a common concern about safety and fraud protection”.⁴⁵ As in Britain, initial legislation focused on ensuring the product’s quality by preventing harmful adulteration or modification of products sold to the public. The *Inland Revenue Act*⁴⁶ of 1875 set the first domestic standards determining what could be added to new products (specifically prohibiting alcohol) before they entered the market. The *Adulteration Act of 1884*⁴⁷ set additional

⁴⁰(1860) 23 & 24 Vict., c. 84

⁴¹*Ibid.*

⁴²*An Act to Amend the Law for the Prevention of Adulteration of Food and Drink and Drugs* (1872) 35 & 36 Vict., c. 74.

⁴³*Steib, supra* note 39 at 23.

⁴⁴*The Sale of Food and Drug Act* (1875) 38 & 39 Vict., R-U., c. 63.

⁴⁵*Steib, supra* note 39 at 216.

⁴⁶*Inland Revenue Act* of 1875, S.C. 1874, c. 8.

⁴⁷*An Act to Amend and to Consolidate as Amended the Several Acts Respecting the Adulteration of Food and Drugs* S.C. 1884 c. 34

standards for strength, quality, and purity of new products to be consumed and made it a criminal offence to manufacture or sell “adulterated food and drugs”.⁴⁸

In 1919 the federal government established the Food and Drugs Division to administer the *Adulteration Act*.⁴⁹ The following year, in 1920, the Canadian Parliament repealed the *Adulteration Act* and passed the *Food and Drug Act*⁵⁰ (FDA). This first incarnation of the FDA focused on the ‘misbranding’ of food and drug products, and sought to reduce the hazards posed by false and misleading claims on drug labels. In 1927 this Act was amended to include supervision of products of animal origin, vaccines and serums and allow for the inspection of premises in which the manufacture of these products occurs.⁵¹ In 1939 further amendments to the *Food and Drug Act* allowed the federal government to make regulations related to the sale of drugs which were “likely to be injurious to the public”.⁵² The government targeted potentially injurious products with especially stringent regulations. In 1946 this power was expanded to allow for the setting of regulations that define “the conditions of sale of *any* drug in the interest of or for the protection of public health”.⁵³

⁴⁸*Ibid.*

⁴⁹Health Canada, *Our Science Our Health: A Report from the Health Products and Food Branch – 2003* (Ottawa: Health Canada, Health Products and Food Branch, 2003) [Our Science Our Health].

⁵⁰*Food and Drug Act*, S.C. 1920 c. 27.

⁵¹See R. E. Curran, *Canada’s Food and Drug Laws* (Chicago: Commerce Clearing House, 1953) [Curran]

⁵²*Ibid.*

⁵³*Ibid.*

(d) Toward Regulating Safety and Efficacy

Fears in the United States stemming from the release of several unproven and toxic drug formulations led Congress to pass the 1938 *Federal Food Drug and Cosmetics Act*.⁵⁴ This legislation gave U.S. regulators the power to require that all new drug products be tested to ensure safety. During this period there was no similar testing of all drugs for safety in Canada. This led to concerns that “Canada was being used as a proving ground for foreign, mostly American, manufacturers to test-market their new drugs”.⁵⁵ In 1951 the federal government passed legislation that required the demonstration of a drug’s safety before it could be marketed.⁵⁶ For the first time, drug manufacturers were required to submit this information to the Food and Drugs Division of the Department of Health and Welfare.

Canada was slow to implement its own guidelines on testing for safety and efficacy until the Thalidomide disaster of the 1960s. Up to that point Thalidomide had been given to pregnant mothers to treat morning sickness, causing physical deformities in their new born infants.⁵⁷ After the dangers of the drug were identified, governments worldwide scrambled to introduce legislation that required drugs to have some demonstrated standard of efficacy (useful clinical indication) paired with safety. In 1963 Canadian law was changed to require “substantial evidence of the clinical effectiveness

⁵⁴*Federal Food, Drug and Cosmetic Act of 1938*, Pub. L. 75-717, 52 Stat. 1041, 12 U.S.C. 301.

⁵⁵J. Lexchin, *The Real Pushers: A Critical Analysis of the Canadian Drug Industry* (Vancouver: New Star Books, 1984) at 183 [Pushers].

⁵⁶*Curran*, *supra* note 51.

⁵⁷A. Dally, “Thalidomide: Was the Tragedy Preventable?” (1998) 351 *The Lancet* 1591.

of the new drug...under the conditions of use recommended”.⁵⁸ In 1967 the standard was enhanced to require the submission of a product monograph, which gave detailed information about the manufacture, composition, risks, benefits, and recommended uses of the product.⁵⁹

The 1951 and 1963 changes to the law pairing safety with demonstrations of efficacy led to the modern clinical trial.⁶⁰ Prior to these legislative initiatives, drugs had been tested mainly through case studies and trial and error. The 1963 amendments required that systematic tests be conducted in a manner that demonstrates clinical effectiveness, a standard that required that new trials provide a comparison with some existing treatment or to no treatment at all. These amendments also ushered in the era of the modern, large, and multi-phased clinical trial. The resulting research model was the *randomized control trial*, in which participants were randomly assigned to either a treatment group administered the new product, a treatment group administered an existing product, or to a placebo group.⁶¹

⁵⁸Health Canada, Progressive Licensing Project, *Progressive Licensing Framework: Concept Paper for Discussion* (Ottawa: Health Canada, 2006) at page 3, online: <http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/develop/proglic_homprog_concept-eng.php> [PL Concept Paper].

⁵⁹*Ibid.*

⁶⁰*Our Science Our Health*, *supra* note 49.

⁶¹Health Canada, *Review of Canada's Regulatory Framework for Clinical Trials: E-Consultation Health Canada* (Ottawa: Health Canada, 2006) at page 5, online: <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e-consultation-eng.pdf> [CTR Review].

(e) *The Arrival of Clinical Trials and Ethical Guidelines*

Initially there were few coherent standards overseeing how clinical trials were conducted. Early clinical trials were criticized for their organization and administration.

As Health Canada itself admits:

The regulatory requirements respecting...clinical trials were originally developed in the early 1960s under the *Food and Drugs Act* (FDA). Over time, the *Act* and attendant regulations became layered with a series of policy and guidance documents, which contained some gaps in enforcement, scope and process given the changing environment of clinical trials and drug development in Canada.⁶²

These gaps did little to ensure the quality of the clinical trial conducted or codify the research done to establish safety and the rights of participants.

The 1948 *Nuremberg Code*⁶³ established “the requirement of voluntary informed consent of the human subject that protects the right of the individual to control his own body”.⁶⁴ This ethical requirement was reinforced by the 1964 *Declaration of Helsinki*,⁶⁵ which sought to protect the basic rights of research participants and ensure that science was not conducted at the expense of subjects. Still, during much of this early period of clinical testing:

⁶²*Ibid.*

⁶³“Permissible Medical Experiments” Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. Nuremberg October 1946 - April 1949, Washington. U.S. Government Printing Office (n.d.), vol. 2., pp. 181-182.

⁶⁴*Ibid.*

⁶⁵World Medical Association, *Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects*, Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, and the 35th World Medical Assembly, Venice, Italy, October 1983, in (1997) 277 *JAMA* 925 and M. Munden, “Ethical Conduct of Human Research Part1: The Declaration of Helsinki” (2004) 4(5) *Clinical Researcher* 2.

Canadian regulations [were] silent on the question of who can and cannot be used as research subjects, and on the necessity of obtaining a subject's informed consent prior to participation in a drug study.⁶⁶

This led to a gap in the rights of those participating in clinical research.

In 1979, the U.S. Commission for the Protection of Human Subjects of Biomedical and Behavioural Research released the *Belmont Report*,⁶⁷ which called for recognition of human subjects in research, beneficence (securing of the subject's ethical and physical well-being), and justice (requiring that the benefits and burdens of research be equitably distributed). This report had a widespread effect on health research regulators and ethicists around the world. In Canada, a variety of institutions and researchers began to incorporate these ethical recommendations into practice. In 1987 the Medical Research Council (MRC) of Canada produced the *Guidelines on Research Involving Human Subjects*.⁶⁸ In 1998 many of these practices were incorporated into the *Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans* (TCPS).⁶⁹ One of the major stipulations of the TCPS was to make explicit that all research conducted in institutions receiving funding from the three national research funding agencies be reviewed by Research Ethics Boards (REB) which oversee the safety and consent rights of study participants.

⁶⁶*Pushers*, *Supra* note 55 at 171.

⁶⁷Government of the United States of America, Department of Health, Education and Welfare, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Washington: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979). [Belmont Report].

⁶⁸Canada, Medical Research Council of Canada, *Guidelines on Research Involving Human Subjects* (Ottawa: Supply and Services Canada, 1987) [MRC Guidelines].

⁶⁹Canada, Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada & Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa: Panel on Research Ethics, 2005), [TCPS].

Partially in response to international pressure to harmonize their approval process,⁷⁰ and partially in recognition of the remaining gaps, the *Food and Drug Act Regulations*⁷¹ (FDAR) were amended on September 1, 2001 by the addition of the *Division 5 - Clinical Trial Regulations*.⁷² These changes had the objectives of “strengthen[ing] protections for human research participants; and attract[ing] sustained investment in research and development in Canada”.⁷³ They set out in detail the administrative and data submission processes that were required of clinical trial researchers, and attempted to standardize the methods for meeting safety and efficacy standards.

(f) Present Policy Initiatives and the Future of Drug Regulation

In 2002 the federal government pledged \$190 million over five years to “speed up the regulatory process for drug approvals to ensure that Canadians have faster access to the safe drugs they need”.⁷⁴ This funding introduced the *Therapeutic Access Strategy (TAS)* as well as a push toward greater integration with international approval standards. The majority of the funds that have been allotted toward the TAS have gone to speeding up approval times and increasing the availability of new drugs.

⁷⁰See J. Lexchin, “Intellectual Property Rights and the Canadian Pharmaceutical Marketplace: Where Do We Go From Here?” (2005) 35(2) *Int. J. Health Services* 237 (WL) [Lexchin Where], also see A. X. Fellemeth “Secrecy, Monopoly, and Access to Pharmaceuticals in International Trade Law: Protection of Marketing Approval Data Under the TRIPs Agreement” (2004) 45 *Harv. Int’l L. J.* 443 (WL) [Fellemeth].

⁷¹*Food and Drug Regulations*, C.R.C. c. 870 [FDAR].

⁷²*Ibid.* at Division 5.

⁷³*CTR Review*, *supra* note 61.

⁷⁴Government of Canada, Department of Finance, *Building the Canada we Want: Budget 2003: Investing in Canada’s Health Care System* (Ottawa: Department of Finance, 2003), online: < <http://www.fin.gc.ca/budget03/booklets/bkhea-eng.asp>>.

In April 2004 Canada and the United States signed a memorandum of understanding that pushed for a closer association and a common process of drug review.⁷⁵ As one author has noted:

The agreement is intended to reduce bureaucratic hurdles for manufacturers applying to have new drugs approved in both jurisdictions, and to bring new drugs to market faster.⁷⁶

The *North American Free Trade Agreement* (NAFTA) and the *World Trade Organization* (WTO) have limited the ability of Canada to produce approval standards which are greater than other G8 trading partners.⁷⁷

Under the new Government of Canada (the Conservative minority mandate began in 2006), several broad health reforms have been initiated which have the potential to influence drug regulation.⁷⁸ The *Blueprint for Renewal: Modernizing Canada's Regulatory System for Health Products and Food* (*Blueprint for Renewal*) is a broad policy mandate that Health Canada has undertaken which seeks to overhaul much of its present regulatory oversight.⁷⁹ With over thirty separate initiatives, it touches on a broad collection of mandated activities, the core objectives being to modernize and integrate these practices with other global partners. Two of these initiatives have specific relevance for the present discussion. The *Progressive Licensing Framework*⁸⁰ (PLF) is an

⁷⁵See B. Purchase, "Canada-US Regulatory Co-Operation" (2004) 171 *CMAJ* 121(PUBMED).

⁷⁶L. Egertson, "Drug Approval System Questioned in US and Canada" (2005) 172(3) *CMAJ* 317 (PUBMED).

⁷⁷*Marrakesh Agreement Establishing the World Trade Organization, Annex 1C: Agreement on Trade Related Aspects of Intellectual Property Rights*, Article 39.3, 15 April 1994, 1869 UNTS 299; 33 ILM 1197 (1994) [TRIPS] and *North American Free Trade Agreement Between the Government of Canada the Government of Mexico and the Government of the United States*, 17 December 1992, Article 1711, Can. T.S. 1994 No.2 (entered into force 1 January 1994) [NAFTA].

⁷⁸These initiatives will be discussed in greater detail in Chapter 4.

⁷⁹*Blueprint*, *infra* note 559.

⁸⁰*PLF Website*, *infra* note 550.

initiative currently underway to revamp the approval process of new drugs to account for “the full life-cycle of a drug, rather than placing the focus primarily upon pre-market assessment”.⁸¹ The *Review of the Clinical Trial Regulatory Framework*⁸² (CT-Div 5 Review) is a mandated review to “ensure that the clinical trial regulatory framework is flexible, robust, and able to respond to emerging scientific trends”.⁸³

The expectation is that these policy changes will increase the accuracy of the safety and efficacy data from clinical trials while enhancing the protections accorded to participants, but this is not certain. As the editors of the CMAJ note:

[Health Canada’s] current emphasis on partnerships with industry and rapid drug approval conflicts with the public’s expectation that these agencies exist to protect them by restricting approval to drugs that have been thoroughly tested and are likely to be free of serious risks.⁸⁴

As the VIGOR example shows, there is still a broad capacity for researchers to seek and regulators to allow approval on the basis of poor data and research.⁸⁵

Setting the Stage: The Law and Institutional Players in Drug Approval

A starting point for any critical analysis of difficulties facing the modern drug review procedure is to introduce some of the institutions, laws, and supporting materials that create the context in which this process unfolds. From their earliest development, pharmaceuticals are subject to a set of rules (laws and policy) and actors (institutional and regulatory) that guide how drug science and approvals unfold. As Dr. Jerry Avorn states

⁸¹*PL Concept Paper, supra* note 58.

⁸²*CTR Review supra* note 61.

⁸³*Ibid.* at 1

⁸⁴*Vioxx Lessons, supra* note 20.

⁸⁵*Ibid.*

in his critical analysis of drug regulation, *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs*.⁸⁶

...the system shapes decisions for good or for ill – the incentives that drive behavior, the culture of expectations about information or standards of practice, the regulations that do or don't exist and how thoughtfully they're enforced.⁸⁷

Government and regulators play a key role in the system by establishing and reinforcing the parameters under which this process unfolds. As Wiktorowicz notes:

... by facilitating some courses of action or making others more difficult, government institutions shape the manner and degree to which organized interests exert influence and thus determine where the balance lies between interest group demands and the programmatic goals of government.⁸⁸

This structure has been created by rational actors through intentional decision-making, and in the process has allowed for the institutionalization of biases that distort the assessment of new drugs.

(a) Law Overseeing Drug Regulation

The law governing pharmaceuticals is a patchwork of provincial and federal legislation and regulations. Provincial governments generally regulate the prescribing and pricing of new drugs while federal law oversees the production, approval, and marketing of pharmaceuticals. The FDA⁸⁹ is the central piece of federal drug legislation. The FDA sets standards for the marketing, production, advertising, and enforcement of

⁸⁶ *Avorn, supra* note 34.

⁸⁷ *Ibid.* at 18.

⁸⁸ *Wiktorowicz, supra* note 24 at 618.

⁸⁹ *Food and Drug Act*, (1985) R.S.C. c. F-27 s. 30 [FDA].

safety criteria. The FDA is supplemented by the FDAR.⁹⁰ Part C of the FDAR addresses the administration, institutional oversight, classification, and marketing of drug products. The *Patent Act*⁹¹ outlines the considerable intellectual property rights accorded pharmaceutical products. The *Notice of Compliance Regulation*⁹² (NOCR) tries to balance the exclusive marketing period of first-entry patent applicants against the rights of generic manufacturers to produce these drugs once patent periods expire. The *Patented Medicines Regulations*⁹³ (PMR) give guidance on the reporting of pricing and expenditures related to research and development undertaken on drugs in Canada.

(b) Defining a Drug

A wide variety of products could be considered drugs for the purpose of this thesis. The FDA specifies that a drug is:

Any substance or mixture of substances manufactured, sold or represented for use in:
the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or its symptoms, in human beings or animals, restoring, correcting or modifying organic functions in human beings or animals, or
disinfection in premises in which food is manufactured, prepared or kept.⁹⁴

This definition encompasses almost any product that can be introduced into the human body for medicinal or therapeutic purposes. For the purpose of my thesis, I will limit the definition of ‘drug’ to include only pharmaceuticals for which pre-approval clinical trials

⁹⁰FDAR, *supra* note 71.

⁹¹R.S.C., 1985, c. P-4 [Patent Act].

⁹²*Patented Medicines (Notice of Compliance) Regulations*, SOR/ 93-133.

⁹³*Patented Medicines Regulations*, SOR/ 94-688.

⁹⁴FDA, *supra* note 89 at s. 1.

are required, in order to focus on the difficulties that result from pre-approval research into these products.

(c) Law and Supporting Materials Regulating Clinical Trials

There are several statutes and codes that touch on the administration of clinical trials. The *Regulations Amending the Food and Drug Regulations (1024 – Clinical Trials)*,⁹⁵ also known as *Division 5*, standardized the format and application requirements for researchers conducting clinical trials. *Division 5* in turn makes reference to the *International Covenant on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*⁹⁶ (ICH), a set of standardized methodological considerations for clinical trials that conform to good clinical practices. The ICH guidelines are to be considered ‘non-binding’ guidance for industry.⁹⁷ The *Tri-Council Policy Statement*⁹⁸ (TCPS) is a set of procedural and substantive ethical rules that must be met to receive funds from one of the three main federal governmental research granting agencies.⁹⁹ Added to these guidelines are a host of provincial and institutional rules, policies, and practices which are applied to research.¹⁰⁰

⁹⁵*FDAR*, *supra* note 71 at Division 5.

⁹⁶Health Canada, Health Products and Food Branch, *ICH* (Ottawa: Health Canada) online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/index_e.html>, accessed June 1, 2006.

⁹⁷*Ibid.* It should be noted that the ICH guidelines are used by the Health Products and Food Branch Inspectorate for compliance enforcement, but compliance actions taken against a drug trial will usually result from harm or danger to the participants, not poor methodology. See the updated Health Canada, *Guidance on: Classification of Observations Made in the Conduct of Inspections of Clinical Trials* (Ottawa: Health Canada, 2008), online: <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/docs/gui_0043_tc-tm-eng.php>.

⁹⁸*TCPS*, *supra* note 69.

⁹⁹*Ibid.*

¹⁰⁰For a good review see M. Hadskis, “The Regulation of Human Biomedical Research in Canada” in J. Downie, T. Caulfield & C. M. Flood, eds., *Canadian Health Law and Policy*, 3rd ed. (Markham: LexisNexis Canada Inc., 2007) [Hadskis].

(d) *Institutional Actors*

Health Canada is the arm of the federal government that oversees the regulation of matters related to public health.¹⁰¹ Within Health Canada, the Health Products and Food Branch (HPFB) is responsible for overseeing the safety of products consumed by the public and meets this responsibility by “managing the health-related risks and benefits of health products and food”.¹⁰² Four branches of the HPFB are concerned directly with medicinal products, the Biologics and Genetic Therapies Directorate (BGTD), the Natural Health Products Directorate (NHPD), Medical Devices Directorate (MDD) and the Therapeutics Product Directorate (TPD). The TPD is the body that approves new drugs and evaluates the quality of pharmaceuticals. The Marketed Health Products Directorate (MHPD) is a directorate of the HPFB which oversees the marketing and safety of a product once it has been approved. Industry Canada oversees the administration of the *Patent Act* while the Patented Medicines and Price Review Board (PMPRB) reports to Industry Canada regarding the appropriate pricing of new drugs. Institutional REBs operate at diverse institutions, both private and public, to oversee the application of the TCPS and the legislative or institutional ethics guidelines for the conduct of research on humans.¹⁰³

¹⁰¹Health Canada, *About Health Canada* (Ottawa: Health Canada, 2006) online <<http://hc-sc.gc.ca.com>>, accessed June 01, 2006.

¹⁰²*Ibid.*

¹⁰³See *Hadskis*, *supra* note 100.

From Birth to Death: The Life-Cycle of a Prescription Drug

Broadly, the release of a new drug can be conceived as occurring in three stages: (1) research and development or ‘pre-approval’, (2) regulatory assessment or ‘approval’, and (3) drug release to the market or ‘post-approval’. In the initial research or pre-approval stage, a product is discovered, studied for potential uses, and clinical trials are completed in anticipation of its regulatory approval. At the assessment stage, industry-submitted research data is reviewed before a decision is made to either approve or deny the drug’s release. This process occurs at the TPD. The final marketing or post-approval stage is the extended period in which the product is released for prescription to the general public. This phase is overseen by the MHPD, which is responsible for assessing the occurrence of adverse events and overseeing the safety of drugs on the market.

(a) Stage 1: Pre-Approval

(i) Discovery

A new drug begins with an idea. This entails either the identification of a potentially useful new compound (a New Chemical Entity [NCE]) or the recognition that a drug is required to address a pressing medical need which leads to a program of research. This ‘need’ may be driven by attempts to treat a known condition or by perceived or created demand for a new treatment.¹⁰⁴ At this stage, funding into the research for developing new drugs is given priority.¹⁰⁵ Some of the funding for new drug

¹⁰⁴See *Overdosed*, *supra* note 23.

¹⁰⁵M. Angell, *The Truth About the Drug Companies: How They Deceive us and What to do About it*, (New York: Random House, 2004) [Angell].

identification comes from private industry but it is estimated that the majority of the research into NCE occurs in public institutions.¹⁰⁶ In Canada the major funding institutions relevant to drug development include the Canadian Institute for Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC), and Industry Canada.

Once a potential NCE has been identified, a decision is made either to develop the product or not. Most decisions as to whether or not to proceed with development of a NCE into a drug are firmly at the discretion of manufacturers. Industry will usually assume control of the product from the original scientist, partnering with researchers or purchasing the product outright. Manufacturers will base this decision on the potential value, effectiveness, marketability, and usefulness of a new drug.¹⁰⁷ This has led to a glut of drugs similar to those already proven profitable on the market, dubbed ‘me-too’ drugs. It is at this stage that the initial filing of a patent can occur.¹⁰⁸ In Canada pharmaceuticals are given a 20-year term for market exclusivity from the date of this filing.¹⁰⁹

(ii) Pre-Clinical Testing

Once the decision has been made to develop an NCE into a new drug, it is first chemically isolated and purified. It then proceeds into a stage of pre-clinical testing to fully determine its chemical properties and toxicity. Studies will be conducted in vitro,

¹⁰⁶*Ibid.*

¹⁰⁷*Ibid.*

¹⁰⁸*Ibid.*

¹⁰⁹*PMR, supra* note 93.

comparing the effect of the drug on healthy and unhealthy living cells. With positive results, animal testing will be conducted to determine the drug's effect on living organisms and to further determine potential toxicity. Animal testing will also attempt to determine whether the product undergoes any metabolic changes when introduced to a functioning physiology in order to establish dosage-related effects and any other unknown side effects.¹¹⁰

If pre-clinical trials demonstrate the potential viability of a new drug, researchers will seek to test the safety and effectiveness of the drug in humans. Manufacturers will submit an *Investigational New Drug Submission* (IND) to the appropriate branch of the TPD (drugs may need to be submitted to the Bureau of Pharmaceutical Assessment, Bureau of Biologics, or Bureau of Radiopharmaceuticals). The IND will need to provide a detailed description of the intended program of research, and the conditions under which it will be conducted. Normally, this information will include: (i) the results and implications of all previous tests, (ii) names of institutions and qualified investigators who will be conducting the research, (iii) approvals from institutional ethics boards, (iv) description of the nature and design of the research to be conducted, and (v) a host of other administrative and manufacturing details.¹¹¹ Typically the TPD will approve or reject an IND within 60 days. If approved, the manufacturers are given the right to provide the drug directly to the researchers named in the IND.

¹¹⁰Chow, *infra* note 196.

¹¹¹Health Canada, *Preparation of Human New Drug Submissions* (Ottawa: Health Canada, 1991), online: <<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/newdrug-drogrouv/prephum-eng.php>> [Reviewed].

(iii) Clinical Trials

Traditionally, clinical trials are conducted in three or occasionally four phases. Phase I trials are early research studies on humans that assess the effects of the drug on a small sample of healthy volunteers. This stage seeks to determine the general absorption, toxicity, metabolism, tolerance, dosage range, and side effects of the drug in humans. In Phase II trials the drug is tested in a larger sample and targeted at specific conditions. The primary aim of this phase is to determine whether the drug is effective in treating specific illnesses, provide information as to the optimum dosage for treatment, and identify any as yet undetermined side effects. Phase III trials are usually large-scale trials designed to test the effect of the drug in a wider population with more participants and in comparison with existing therapies. Phase III trials also serve as the chief demonstration that the drug has some therapeutic value in treating a specific condition in a targeted population. Phase IV trials will be discussed later in the post-approval stage.

(b) Stage 2: Approval

(i) New Drug Submission

Once researchers feel that they have gathered sufficient data to justify the product's approval, they will file a *New Drug Submission* (NDS) with the Therapeutic Products Programme's Submission and Information Policy Division of the TPD. According to Health Canada, this justification is provided through evidence and/or studies that "prove the drug has potential therapeutic value that outweigh the risks

associated with its use”.¹¹² The NDS must include: (i) details about the intended name, branding, and claims to be made of the new product, (ii) reports describing the studies conducted to establish the product’s safety and efficacy, (iii) a description of those overseeing the research, (iv) methods associated with the product’s manufacturing and chemical contents, and (v) any other details of the new product.¹¹³

The TPD will then assess submitted data to determine whether the product should be approved or not. The mechanics and considerations employed in this process are not fully known. Due to intellectual property law, the data submitted by industry towards approval is protected as proprietary knowledge and as a result the process is not open to the public. Health Canada indicates that the TPD goes through at least four stages in considering the industry submissions.¹¹⁴ First the TPD reviews all of the submitted information, calling on external experts or forming advisory committees if necessary. Next, officials at the TPD evaluate the “safety, efficacy and quality data to assess the potential benefits and risks of the drug”.¹¹⁵ They then look at the information that the manufacturer intends to provide to health-care providers including labelling, the product monograph, and brochure. Finally, if “at the completion of the review, the conclusion is that the benefits outweigh the risks and that the risks can be mitigated”,¹¹⁶ the drug is approved.

¹¹²*Ibid.*

¹¹³*Reviewed, supra* note 111.

¹¹⁴*Ibid.*

¹¹⁵*Ibid.*

¹¹⁶*PL Concept Paper, supra* note 58, at page 19.

(ii) Drug Identification Number and Notice of Compliance

Upon a drug's approval Health Canada will issue a Drug Identification Number (DIN) and *Notice of Compliance* (NOC) to the manufacturers. Only one DIN can be issued per drug and it enables the manufacturer to exclusively sell the product.¹¹⁷ The NOC provides the additional protection of sole right to market the product in Canada. The TPD can approve a drug with specific conditions that will apply to its use, called a *Notice of Compliance with Conditions* (NOCc). If an application is found to be incomplete, a *Notice of Deficiency* (NOD) will be issued and applicants may amend their applications. If the application is rejected outright, a *Notice of Non-Compliance* (NONC) will be issued. In the case of a NONC being issued, drug companies can re-apply for approval by submitting an *Amended New Drug Submission* (ANDS) as many times as required until approval is obtained.

(iii) Special Access and Priority Review

Drugs may be approved without a full review if they are needed to treat an immediate or urgent medical need. Under the *Priority Review of Drug Submission Policy*,¹¹⁸ a new product may be fast-tracked for approval if it provides treatment for a “serious, life-threatening or severely debilitating illness or condition”¹¹⁹ for which there is no existing treatment in Canada or if it has the potential to be more effective than

¹¹⁷FDAR, *supra* note 71 at s. C.01.014

¹¹⁸Health Canada, *Priority Review of Drug Submissions Policy*, (Ottawa: Health Canada, 2009), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/prds_tppd_pol-eng.php> [Priority Review].

¹¹⁹*Ibid.*

existing therapies. If a drug is accepted for priority review, it will be assessed for approval in 180 days.

Drugs may also be approved without a full review for a limited and specific use, using the Special Access Program (SAP).¹²⁰ Special access to a drug may be allowed for patients “with serious or life-threatening conditions on a compassionate or emergency basis when conventional therapies have failed, are unsuitable, or are unavailable”.¹²¹ The SAP does not allow for a product to receive general approval beyond its limited use but it may serve as a mechanism for introducing specific drug therapies.

(c) Stage 3: Post-Approval Stage

(i) Drug Pricing

Before a product is placed on the market, a determination must be made as to its price. Pricing is set by the Patented Medicines Price Review Board (PMPRB), a quasi-judicial body convened under the *Patent Act*.¹²² The five-member panel is responsible for assessing the price at which companies propose to whole-sale drugs to pharmacies. Section.85(1) of the *Patent Act*¹²³ outlines a series of factors that the PMPRB can consider in making its pricing decisions, including the price of similar products in Canada and the price of the product in different countries. If the drug is relatively novel to the Canadian market, this may lead to decisions on the basis of “the cost of making and

¹²⁰*FDAR, supra* note 71 at s. C.08.010(1)

¹²¹Health Canada, *Special Access Programme - Drugs*, (Ottawa: Health Canada, 2005), online: <http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogués/sapfs_pasfd_2002-eng.php> [Special Access Programme].

¹²²See *Patent Act, supra* note 91, at s. 79-100.

¹²³*Ibid.*, s. 85(1).

marketing the medicine”.¹²⁴ In theory, the PMPRB will periodically review this pricing but seldom will it ask a drug manufacturer to reduce the price at which it is selling its product.

(ii) Drug Scheduling

In Canada there are four different schedules for drugs. Schedule I drugs are available only by prescription and must be provided by a pharmacist. Schedule II drugs are available from a pharmacist but must be kept in a location without public access. Schedule III drugs are available ‘over the counter’ or without supervision in any pharmacy.¹²⁵ Unscheduled drugs can be sold in any store, without supervision. The National Drug Scheduling Advisory Committee (NDSAC) makes recommendations to each province on how to schedule prescription drugs and works with the National Association of Pharmacy Regulatory Authorities (NAPRA) to establish national standards of drug scheduling.

(iii) Listing in Provincial Formularies

Provincial governments determine whether drugs will be covered by provincial health plans by listing them on provincial formularies. As one author has noted:

¹²⁴*Patent Act*, *supra* note 91 at s. 85(2).

¹²⁵See Canada, National Association of Pharmacy Regulatory Authorities (NAPRA), *NDS-Overview: Outline of the Schedules*, (Ottawa: NAPRA, 2009), online: < http://www.napra.org/Content_Files/Files/Schedules-Outline.pdf> [NAPRA].

provincial governments have no jurisdiction over market competitiveness or pricing, yet they end up paying for most of the drug expenditures incurred.¹²⁶

What is included on a provincial formulary varies widely across the country. Many of these decisions are guided by a “cost effectiveness analysis”¹²⁷ that determines the potential benefit of the drug offset by its cost. There is a push for drugs to undergo a Common Drug Review (CDR) at the federal level to create recommendations as to what should be included on provincial formularies. This process is guided by the Health Canada-funded Canadian Agency for Drugs and Technology in Health (CADTH) (formerly the Canadian Coordinating Office for Health Technology Assessment [CCOHTA]), which in turn relies heavily upon recommendations from the Canadian Expert Drug Advisory Committee (CEDAC). However, adherence is not uniform; Quebec does not partake in the CDR process and most provinces pay only partial attention to CADTH recommendations.¹²⁸

(iv) Monitoring Drug Safety at the Marketed Health Products Directorate

Once a drug is approved and made available to the public, the MHPD is responsible for overseeing its safety. The MHPD is charged with “post-approval safety surveillance, assessment of signals and safety trends, and risk communications

¹²⁶See A. H. Anis, “Pharmaceutical Policies in Canada: Another Example of Federal-Provincial Discord” (2000) 162(4) *CMAJ* 523 (PUBMED).

¹²⁷*Ibid.* at 523.

¹²⁸A. H. Anis, D. Guh & X. Wang, “A Dog’s Breakfast: Prescription Drug Coverage Varies Across Canada” (2001) 39(4) *Medical Care* 315 (JSTOR).

concerning all regulated marketed health products”.¹²⁹ The MHPD is responsible for keeping track of any significant international and domestic adverse drug reports or product recalls, and relaying this information to medical practitioners. Additional Phase IV Trials may be completed after a product is on the market to confirm its long-term safety or to investigate alternative uses than those for which it was approved. Reporting of unexpected adverse events is overseen by the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) and recorded on the *Canadian Adverse Drug Reaction Information System (CADRIS)*.¹³⁰

(v) Prescriptions and the Administration of Release

The administration of new drug releases and the laws which oversee the prescribing and filling of prescriptions are under provincial authority. Most medications require a prescription, with the exception of samples which in turn will be filled by a qualified pharmacist.¹³¹ Provincial health Acts and legislation regulating the admission to the health professions give some guidance as to who may write and fill prescriptions, but there is little oversight of the discretion that doctors use in deciding to prescribe a medication.

¹²⁹Health Canada, *About Health Canada: Marketed Health Products Directorate* (Ottawa: Health Canada), online: Health Canada <http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/mhpd-dpsc/index_e.html>.

¹³⁰See the Health Canada, *Canada Adverse Drug Reaction Monitoring Program – Database* (Ottawa: Health Canada) online: <http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index_e.html>, accessed March 12, 2006.

¹³¹*NAPRA*, *supra* note 125.

The prescribing practices of doctors are an intensive focus for the marketing activities of drug companies. This marketing is usually done directly by advertising in medical journals and to patients, as well as indirectly by educating physicians¹³² and sponsoring the publication of favourable studies. Regulation of advertising is technically under the authority of the FDA (s.9) and the TPD, but in the policy document *The Distinction between Advertising and Other Activities*,¹³³ Health Canada has limited the nature of what it considers advertising to only the most overt forms of commercial representation. The oversight of advertising practices is in the hands of three non-governmental bodies: Advertising Standards Canada (ASC), the Pharmaceutical Advertising Advisory Board (PAAB), and the pharmaceutical lobby group Rx & D (Canada's research-based pharmaceutical companies).¹³⁴

(vi) *The Expiry of Patents and Generic Drugs*

A drug's patent expires 20 years after its initial filing. In anticipation, s.97 of the *Patents Act* allows generic companies to begin stockpiling supplies of their drug. Once the patent period has expired, generic companies may file an *Abbreviated New Drug Submission* (ANDS) which establishes the drug's bioequivalency to an already existing

¹³²As recently as December 2009, Pfizer announced a \$780,000 CAD fund to help the Canadian Medical Association develop a continuing education program for doctors, see C. Weeks, "Medical Association Takes Heat for Pfizer Funding" *Globe and Mail* (2 December 2009), online: <<http://www.theglobeandmail.com/life/health/medical-association-takes-heat-for-pfizer-funding/article1386224/>>.

¹³³Health Canada, *The Distinction Between Advertising and Other Activities* (Ottawa: Health Canada, 1996), online: <http://www.hc-sc.gc.ca/dhp-mps/advert-publicit/pol/actv_promo_vs_info_e.html>, accessed March 11, 2006 [Distinction].

¹³⁴P. C. Hebert, "Direct-to-Consumer Advertising: End the Compromise" (2008) 179(2) *CMAJ* 119 (PUBMED).

product.¹³⁵ The thrust of an ANDS is not additional demonstration of drug safety or efficacy but merely the demonstration that the product is chemically equivalent to the product whose patent is about to expire. Under s.7(1) of the *Patented Medicines Regulations*, an extension of 24 months may be granted to a patent holder if they object to another manufacturer's ANDS. By slightly modifying their original drug (i.e. Schering's Claritin, ClaritinExtra and Aerius or Wythe's Effexor and EffexorXR) or by objecting to new NOC applications, drug companies are often able to extend the patent life of their drugs by months or even years.¹³⁶ This 'evergreening' allows a pharmaceutical company to use the patent law to perpetuate their patent exclusivity.

(vii) *Disposal*

The final question for any pharmaceutical product is the issue of disposal. As pharmaceuticals make their way through the human body, they are metabolized and eventually released into the environment.¹³⁷ Similarly, unused drugs expire and must also be disposed of in the environment. Recent research has shown that drugs have begun to build up in potentially hazardous quantities in the environment.¹³⁸ This is a potential problem that we have hardly begun to tackle through either science or legislation.

¹³⁵FDAR, *supra* note 71 at C.08.02.1

¹³⁶R. A. Bouchard, R. W. Hawkins, R. Clark, R. Hagtvedt & J. Sawani, "Empirical Analysis of Drug Approval-Drug Patenting Linkage for High Value Pharmaceuticals" (2010) 8(2) *Northwestern J. Tech. and Intl. Property* 174 (Lexis) [Patent Linkage] and T. A. Fauci & J. Lexchin, "Linkage Pharmaceutical Evergreening in Canada and Australia" (2007) 4 *Australia and New Zealand Health Policy* 8 (WL).

¹³⁷K. Kümmerer ed., *Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks*, 3rd ed. (New York: Springer, 2008) & G.J. Mannina, "Medicines and the Environment: Legal and Regulatory Storms Ahead" (2006) 21(11) *Washington Legal Foundation*, online: <<http://www.wlf.org>>.

¹³⁸*Ibid.*

Science and Law in the Regulatory Process

At each stage indicated above, science, policy, and law overlap to guide and establish the reality in which decisions are made. All three are ever present and adapt to the other to determine how drugs are developed, approved, and ultimately released to the public. Law and policy must look to science to define the parameters of safe practices. Science in turn adapts its questions to suit the demands of those creating, interpreting, and applying the law. It is impossible to separate this interaction, so we must be vigilant that science, policy, or law is not given a position of dominance in guiding the decisions about the ultimate approval of new drugs. We must also be mindful of the inherent biases of these tools to ensure that they do not distort the drug approval cycle.

(a) Science in the Drug Life-Cycle

Essential to any decision-making process is the application of clear, bias-reduced science. In theory, the only way to justify a potentially harmful drug's release is a demonstration that it has potential merit that outweighs its risks. This demonstration of merit must be based on more than unsystematic human supposition or belief. For confidence and certainty in decision-making, we must look to systematic and long-term observations that are bound by rules that seek to standardize results and limit the source of human error in observation. It is hoped that these observations will be accurately relayed to regulators to help guide and inform the review process. We can see the use of science occurring at each of the three stages in the regulatory process.

(i) Science in Pre-Approval

At the research stage, decisions about which drugs and research to sponsor are continually changed by our understanding of disease and how to treat illness. The AIDS drug AZT is a good example. Initially, it was developed for other purposes (an anticancer drug) but was abandoned after initial pre-clinical testing proved too costly and showed poor early results. As the AIDS epidemic came to a head in the mid-to-late 1980s, researchers were scrambling to develop new treatments. New microbiological, metabolic, and genetic techniques in medicine enabled researchers to identify the mechanisms of AIDS. Tackling the illness required changing the disease research paradigm from isolation and immunization to the reduction of impairment. Medical funding models needed to include a much broader range of research into the mechanisms of disease.¹³⁹ It was in this environment that many long abandoned NCEs were reconsidered, such as the precursor to AZT.

(ii) Science in Approval

Science is also crucial to establishing the validity of any decision to approve a new drug. In making these decisions, scientists at the TPD conduct a form of risk assessment that must be based on data that establishes the drug's safety. When science is ignored or undermined in this process, disastrous outcomes can result. Although the conditions of Vioxx's approval in Canada are not known, in the United States, the Food

¹³⁹L. K. Perrin, "The Catch-22 for Persons with AIDS: To Have or Not Have Easy Access to Experimental Therapies and Early Approval for New Drugs" (1995) 69 *Cal. L. Rev.* 105 (HEINONLINE) [Catch 22].

and Drug Administration (FDA) failed to listen to the pleas of its scientists and significant data that hinted at the drug's dangers.¹⁴⁰ In Canada, in one of the few cases where researchers have obtained the data upon which an approval decision was made, this data was made up of a collection of studies whose methodology and results were weak and inconclusive.¹⁴¹ The result was that a potentially dangerous drug was too easily approved. Without reference to well-conducted science, any form of risk evaluation loses its worth. Decisions become subject to political or economic justifications that have little relation to the product's merit.

(iii) Science in Post-Approval

Once a product is released, it is only through systematic observation and evaluation of its long-term safety that it may be judged worthwhile. That a product has been used for years is no proof that it is safe.¹⁴² This product had been used for decades and was only pulled from the market after several deaths demonstrated that the product was potentially dangerous. This form of informed systematic observation will drive drug availability and restriction in the market. Potentially, research and ideas about the value of existing pharmaceuticals are adjusted as new sources of potential harm are recognized. No product can ever be proven completely safe, and it is with vigilant observation that the potential merits and harms of even long-familiar medications are uncovered.

¹⁴⁰J. Avorn, "FDA Standards – Good Enough for Government Work?" (2005) 353(10) *NEJM* 969 (PUBMED) [Standards].

¹⁴¹B. Mintzes, "Drug Regulatory Failure in Canada: The Case of Diane-35" (2004) *Women and Health Protection*, online: <www.whp-apsf.ca>, accessed January 21st 2005 [Mintzes].

¹⁴²*Ibid.*

*(b) Law and Policy in the Drug Life-Cycle*¹⁴³

Going hand in hand with the systematic observations guiding the decision-making process are the laws and policies that clarify and solidify the rules applied to new drug approvals. Law and policy operate at each stage of this process, creating the ways in which regulators and law-makers have decided to address the difficulties and benefits of new drugs. They embody the decisions, compromises, and mechanisms or institutions through which political will is manifest. Law and policy also guide the decisions made by those seeking the approval and marketing of new drugs, setting the stage for how science is to be considered and which issues are assigned the greatest weight in drug safety. Unfortunately, law and policy can often have unintended effects, creating exploitable lacuna where it is silent or papering over areas of needed scientific inquiry.

(i) Law and Policy at Pre-Approval

At the pre-approval research stage, legal rules have served to create both the present research environment and guide what companies consider when undertaking clinical investigation into new drugs.¹⁴⁴ Profitability for new drugs is tied to patent life and marketability, and legislation guiding research funding has tended to highlight

¹⁴³Please note: this thesis will not discuss the civil law as a mechanism for guiding drug approval behavior, (i.e. Tort). Several recent articles have highlighted the ineffectiveness of Tort Law in the circumstances of large drug regulatory failures to serve as a sanction/guide to either regulators or drug manufacturers. Therefore for the scope of this thesis will focus on the obligations nested in statute. See F. M. McClellan, “The Vioxx Litigation: A critical Look at Trial Tactics, The Tort System, and the Roles of Lawyers in Mass Tort Litigation” (2008) 57 *DePaul Law Review* 509 (HEINONLINE) [Vioxx Tactics].

¹⁴⁴See *Wiktorowicz*, *supra* note 24.

innovation and pairing new research with private funding.¹⁴⁵ The sad result is that more ‘me-too’ drugs than truly novel products may be created.¹⁴⁶ Similarly, the legal regime has favoured increasing the speed with which new products are approved. For example, the priority drug-approval initiative was originally designed for the speedier review of truly novel and needed emergency treatments such as AZT.¹⁴⁷ Unfortunately, recent policy developments have expanded the definition of ‘urgent medical need’ to include a host of drugs which are potentially more harmful and less essential, such as Vioxx.¹⁴⁸

(ii) Law and Policy at Approval

Laws protecting the confidentiality of data submitted for approval have created the ‘black box’ that operates at the approval stage.¹⁴⁹ Much of the original approval data for the 41 drugs that were withdrawn from the market from 1963 through to 2004 for safety reasons still remains veiled.¹⁵⁰ This has led to criticism of Canada’s drug regulatory process as “unnecessarily opaque”.¹⁵¹ Or, as one author has noted, “in Canada, decisions to approve a drug are made behind closed doors, without public input or access to the information used in decision-making”.¹⁵² The unconvincing reason for this veil is tied to international trade policy protecting manufacturer data against unfair

¹⁴⁵See *Patent Linkage*, *supra* note 136 also see M. A. Lemley “Are Universities Patent Trolls” (2008) 18 *Fordham Intell. Prop. Media & Ent. L. J.* 611 (HEINONLINE).

¹⁴⁶*Patent Linkage*, *supra* note 136.

¹⁴⁷*Catch-22*, *supra* note 139.

¹⁴⁸A. S. Relman & M. Angell, “America’s Other Drug Problem: How the Drug Industry Distorts Medicine and Politics” (2002) *The New Republic* 27 [Relman] see *Pushers*, *supra* note 55 for Canadian examples.

¹⁴⁹*Oasis*, *supra* note 29.

¹⁵⁰*Lexchin Withdrawal*, *supra* note 18 also see *Mintzes*, *supra* note 141.

¹⁵¹Health Canada, *Science Advisory Board Committee on the Drug Review Process, Report to Health Canada* (Ottawa: Health Canada: 2000), online: <http://www.hc-sc.gc.ca/sr-sr/pubs/advice-avis/sub-css/rep-rap/_archived/dr-pdm-eng.php>.

¹⁵²*Mintzes*, *supra* note 141 at 3.

commercial use.¹⁵³ International trade agreements seek to standardize the criteria that host countries can consider when assessing new drugs for approval.¹⁵⁴ The result is that signatories to many international treaties are limited in the discretion that they can exercise in developing an approval process.

(iii) Law and Policy at Post-Approval

The influence of the law is also apparent at the post-approval stage. The law is vague about the discretion that a physician should use when prescribing a drug. Problematically, a drug can be prescribed for any medically justifiable purpose, regardless of whether it was approved for that purpose, in a practice called *off-label use*.¹⁵⁵ This has spawned the practice of marketing drugs for additional uses to physicians, using a host of activities.¹⁵⁶ Advertising is regulated by the MHPD, but they have been slow to enforce advertising standards.¹⁵⁷ Instead, policy interpretation of the law has sought to rely primarily upon adverse event reporting as a barometer of dangerous prescribing practice.

Law, policy, and science overlap continuously throughout the drug approval process, in theory working together to put in place mechanisms to heighten the safety of products available to consumers. Yet as will be discussed in the following chapters, there

¹⁵³See *TRIPS and NAFTA*, *supra* note 77

¹⁵⁴*TRIPS*, *supra* note 77 at Articles 41, 50 and *NAFTA*, *supra* note 77 at Articles 1701, 1714, 1716.

¹⁵⁵It should be noted that there is potential liability in Tort for off-label use, but increasingly the literature is being critical of the effectiveness of civil remedies in effectively changing/modifying drug use behaviour, see *Vioxx Tactics*, *supra* note 143.

¹⁵⁶*Angell*, *supra* note 105.

¹⁵⁷A. Silversides, "Charter Challenge of Ban on Direct-to-Consumer Advertising to Be Heard in Ontario" (2009) 181(1) *CMAJ* E5 (PUBMED).

are many gaps in the use of science created by the law and many places where science creates ambiguity such that legal and policy judgment must come to bear. It is a very delicate balance ensuring that each is judiciously applied and adapted to the larger goal of ensuring drug safety and efficacy.

CHAPTER 3: REGULATING BIAS, SOUND SCIENCE AND THE CLINICAL TRIAL

Introduction

In the following chapter, I will review the law governing the clinical trial in Canada and demonstrate that the mechanisms in place are inadequate to ensure both patient safety and the conduct of good, methodologically sound research. I will first provide a brief background to the modern clinical trial. Next I will explore some of the elements and biases that can occur in clinical research. Finally, I will appraise the law in place to ensure that good research with robust methodology is being conducted.

TeGenero (TGN-1412): A Costly Lesson in Clinical Research

On March 13, 2006, eight healthy volunteers at the Northwick Park Hospital in London, England took part in what was to be a routine Phase I clinical trial of a new immunoregulatory drug TGN1412 (TeGenero[TeG]). Participants were to be administered the first human exposure to TeG after it had previously been tested for safety on animals. Six of the participants were given a dose of the drug, while two were given the placebo. Within an hour all six subjects administered the drug were experiencing horrific side effects: intense discoloration, sweating, massive swelling of the head and neck, and finally, multiple and system-wide organ failure.¹⁵⁸ TeG had caused an

¹⁵⁸L. Farzaneh, N. Kasahara & F. Farzaneh, “The Strange Case of TGN1412” (2006) 56(2) *Cancer Immunology and Immunotherapy* 129 (PUBMED) [Strange Case].

unforeseen physiological reaction in which the immune systems of participants began to attack their own bodies and reject their organs.¹⁵⁹

Few new drug products prove as lethal a toxin as TeG. It had been tested on a variety of animals in pre-clinical trials, but since it was a drug that affected specific human immune cells (T-cell receptors) it was difficult to extrapolate these results to humans.¹⁶⁰ Furthermore, researchers should have been more cautious in administering high dosages of the drug to multiple patients in the first session without having first used more incremental measures (i.e. as for an allergen, by scraping exposed skin).¹⁶¹ Yet, the spectacular failure of TeG's Phase I trial has ensured that the drug will be restricted from further development and administration to the public.¹⁶² The intended purpose of a Phase I trial has been fulfilled, but at what cost? There are at least two lessons that can be drawn from the TeG clinical trials. The first is that clinical testing can in fact work to detect harm; the second is that the design of trials impacts the outcome of research.¹⁶³

It would be surprising to most Canadians to learn how little is actually known about new drugs by the time they reach their medicine cabinets. In fact, "when a new drug is first marketed, little is [absolutely] proven about its safety and effectiveness compared to existing alternatives".¹⁶⁴ We approve drugs knowing that there is a certain degree of risk. There is no way to ensure with absolute certainty that a drug is completely

¹⁵⁹*Ibid.*

¹⁶⁰*Ibid.*

¹⁶¹M. Goodyear, "Learning from the TGN1412 Trial" (2006) 332 *BMJ* 677 (PUBMED) [Goodyear].

¹⁶²O. Dyer "Firm Involved in Drug Trial Fiasco Files for Bankruptcy" (2006) 333 *BMJ* 114 (PUBMED) [Dyer].

¹⁶³M. Goodyear, "Further Lessons from the TGN1412 Trial: New Guidelines Call for a Change in the Culture of Research" (2006) 333 *BMJ* 337 (PUBMED) [Goodyear – Further].

¹⁶⁴*Avorn, supra* note 34.

safe. Instead, regulators must try to balance harm and benefit based on the best data that is available. Even the best approval decisions must be made on a sampling of clinical observations and, if available, data from other countries where the drug is already on the market.¹⁶⁵ It is impossible to capture a complete ‘real-world’ picture of the effects of a drug before it is marketed. Even accurate observations are no guarantee against isolated adverse reactions that may occur when a drug is given to thousands or even millions of patients.¹⁶⁶

Obtaining the best data implies that we have the best methodology for accurately observing the effects of drugs to approximate the conditions under which they will ultimately be used. As Karl Popper notes in *The Logic of Scientific Discovery*:

There is only one way to make sure the validity of a chain of logical reasoning. This is to put it into a form in which it is easily testable: we break it up into many small steps, each easy to check by anybody who has learned the mathematical or logical techniques.¹⁶⁷

Making approval decisions as accurate as possible supposes regulatory decisions are based on good science (i.e. making claims on safety and efficacy that are objective and well tested, and ensuring that human reasoning is tempered by objective and systematic observation).

¹⁶⁵Reviewed, *supra* note 111.

¹⁶⁶J. LeLorier, “The Science of Health Technology Assessment – Clinical Effectiveness of Therapeutic Interventions” (2001) 8 *Can. J. Clin. Pharmacol.* 21A (PUBMED).

¹⁶⁷Popper, *supra* note 2 at 81.

Toward a Science of Experience and Good Experimental Design

(a) The Early Evolution of Experimental Medicine

So, what are the standards for scientific validity? Even one hundred years ago a product such as TeG might have been sold without any systematic testing for its medicinal value or toxicity. For thousands of years, decisions about which drugs and remedies were applied to illness came from untested experience.¹⁶⁸ Galenic methods relied upon the use of “bleeding, purging and drugs, often in the particularly undesirable form of mixed drugs”¹⁶⁹ to balance the body’s misaligned humours. As Avorn notes:

An apprentice physician was not expected to understand data from experiments, but to memorize concepts and recipes based on arcane humeral relationships, regurgitating the same wrong ideas that had been passed down from physician to apprentice over the generations.¹⁷⁰

Under this method, there were many useless products and treatments dangerously administered and there was little attempt to separate effective remedies from those that might have been toxic.

Beginning with Francis Bacon in *Novum Organum*¹⁷¹ there was a “rediscovery of the necessity of repeated experience and reporting negative facts”.¹⁷² Other theorists, such as Locke,¹⁷³ began to assert that medical practice and the administration of drugs should be based on “actual clinical experience...a theory of experience and animal

¹⁶⁸Ackernecht, *supra* note 31.

¹⁶⁹*Ibid.* at 52.

¹⁷⁰Avorn, *supra* note 34 at 42.

¹⁷¹F. Bacon, *Novum Organum*, (London, 1620) as cited in Lillenfield, *infra* note 176

¹⁷²Ackernecht, *supra* note 31 at 54.

¹⁷³K. Dewhurst, *John Locke (1623-1704): Physician and Philosopher* (London: Wellcome Historical Medical Library, 1963) [Locke].

experimentation therapeutics”.¹⁷⁴ The validity of claims made for treatments needed some justification rooted in systematically repeated observations. As one author notes during early drug use:

What was missing was a systematic way to evaluate a given treatment – not to determine whether it makes sense, since most ineffective treatments make sense in one system of thought or another, but whether it actually works.¹⁷⁵

Researchers needed an easily repeatable and sound method for determining how different treatments compared to one another.

In 1747 a Scottish naval surgeon named James Lind conducted the first recorded comparative experiment of different treatments.¹⁷⁶ Seeking a solution to the age-old difficulty of scurvy (a dietary deficiency of vitamin C on long sea voyages), he decided to try varying the diets of 12 stricken seamen. He placed two patients on six different treatments: cider, elixir vitriol, seawater, vinegar, oranges, and lemons. In reporting his results he observed:

The most sudden and visible good effects were perceived from the use of the oranges and lemons, one of those who had taken them being at the end of the six days fit for duty.¹⁷⁷

The result was the discovery of a simple, effective, and inexpensive treatment for scurvy: the carrying of lemons on long sea voyages.¹⁷⁸ The genius of Lind’s experiment was not that he merely sought to determine the utility of a cure, but to demonstrate that it was more useful than other existing treatments

¹⁷⁴Ackernecht, *supra* note 31 at 55.

¹⁷⁵Avorn, *supra* note 34 at 48.

¹⁷⁶See A. Lillenfield, “Ceteris Paribus: The Evolution of the Clinical Trail” (1982) 56(1) *Bulletin of the History of Medicine* 1 [Lillenfield].

¹⁷⁷J. Lind, *A Treatise of the Scurvy* (Edinburgh: A. Kincaid & A. Donaldson, 1753), online: James Lind Library, University of Edinburgh <<http://www.jameslindlibrary.org>>, accessed May 27, 2006.

¹⁷⁸This ultimately led to the moniker ‘limies’ for British seamen.

(b) Refining the Clinical Trial

It took some time for Lind's methods to take root. Throughout the eighteenth and nineteenth centuries there was a slow refinement of techniques used for comparing various methods of treatment and the gradual introduction of statistics as a mathematical method for quantifying these differences.¹⁷⁹ In 1820, Lois introduced his influential "méthode numérique" that suggested comparisons be made between treatments to validate their use, which codified Lind's methodology.¹⁸⁰ In 1865, Claude Bernard introduced the idea that researchers should try to hold all conditions equal and control between those receiving different treatments, with the exception of those being tested.¹⁸¹ In 1923, Fisher and Mackenzie introduced the idea that conditions being observed should be assigned randomly to one's object of observation, in their case potato crops.¹⁸² In 1931, the first wide-scale observation of varying treatments was completed using the now familiar clinical trial format.¹⁸³ Following the Second World War, it was observed that treatments also needed to be tested against the absence of treatments (i.e., a placebo) to guard against participants' expectations that a treatment is working.¹⁸⁴

¹⁷⁹Lillenfield, *supra* note 176.

¹⁸⁰P. C. A. Lois, *Researches on the Effects of Blood Letting in Some Inflammatory Diseases and on the Influence of Tartarized Antimony and Vesication in Pneumontis*, trans. by C. G. Putnam (Boston: Hillard, Gray, 1836) as cited in Lillenfield, *supra* note 176.

¹⁸¹C. Bernard, *An Introduction to the Study of Experimental Medicine*, trans. by H. C. Greene (New York: Dover Publications, 1957) as cited in *Ibid.*

¹⁸²R. A. Fisher & W. A. Mackenzie, "Studies in Crop Variation II: The Manurial Response of Different Potato Varieties" (1923) 13 *J. Agricultural Science* 311 as cited in *Ibid.*

¹⁸³J. B. Ambersome, B. T. McMahon & M. A. Pinner, "A Clinical Trial of Sanocrysin in Pulmonary Tuberculosis" (1931) 24 *American Review of Tuberculosis* 401 (PUBMED).

¹⁸⁴See L. Lashna, F. Mosteller, J. M. VonFelsinger & H. K. Beecher, "A Study of the Placebo Response" (1954) 16(6) *American J. Medicine* 770 (PUBMED).

(c) Tuskegee and the Limits of Unfettered Scientific Experimentation

While the science of clinical trials was becoming the dominant research model, a troubling incident emerged to highlight the dangers of unfettered clinical observation. In 1932 the U.S Public Health Service (USPHS) began a clinical trial in Tuskegee, Alabama, to determine the long-term course of untreated syphilis on black males.¹⁸⁵ For approximately 40 years, researchers tracked the lives of over 400 poor sharecroppers who were suffering from the disease without providing any intervention. By the 1950s, penicillin had become widely available and accepted as an effective treatment for syphilis, yet researchers still did not tell subjects “they had syphilis, and [they were] not given counselling on avoiding spread of the disease or given treatment”.¹⁸⁶ It was only after the press began to highlight the racist and moral exploitation of the study that it was finally suspended in 1972.¹⁸⁷

The course of this research suggests that unfettered scientific research on humans cannot be justified and that “the notion that science is a value-free discipline must be rejected”.¹⁸⁸ Researchers had intentionally decided to observe the course of this disease in a poor African-American population. This decision was partially based on:

speculation in the scientific literature at that time on racial differences in the natural history of syphilis, including theories suggesting that syphilis

¹⁸⁵For a good description of the course of this experiment, see J. Jones, *Bad Blood: The Tuskegee Syphilis Experiment*, (New York: MacMillan, 1993).

¹⁸⁶G. Corbie-Smith, “Legacy of the Tuskegee Syphilis Study: Considerations for Clinical Investigation” (1999) 317(1) *Southern Society for Clinical Investigation* 5 (PUBMED).

¹⁸⁷A. M. Brandt, “Racism and Research: The Case of the Tuskegee Syphilis Study” in E. J. Emanuel, R. A. Crouch, J. D. Arras, J. D. Moreno & C. Grady eds., *Ethic and Regulatory Aspects of Clinical Research: Readings and Commentary* (Baltimore: The Johns Hopkins University Press, 2003) at 20.

¹⁸⁸*Ibid.* at 23.

affected the neurologic functions of whites and that latent syphilis impaired the cardiovascular system of blacks.¹⁸⁹

This rationale was contrary to the prevalent scientific literature of the day. What the Tuskegee experiment did highlight was that sound methodology must be tempered by moral and ethical consideration; the recognition and incorporation of these concerns into sound experimental administration that protects participants is the second pillar upon which good research must be based.

(d) The Modern Clinical Trial

Legislative changes in the United States and Canada requiring the demonstration of both safety and efficacy introduced the modern era of the large drug trial.¹⁹⁰ A clinical trial can be defined as “a prospective study, comparing the effect and value of intervention(s) against a control in human beings”.¹⁹¹ A more detailed definition is provided by the FDAR:

a research study in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.¹⁹²

¹⁸⁹S. B. Thomas & J. W. Curran, “Tuskegee: From Science to Conspiracy to Metaphor” (1999) 317(1) *American Journal of Medical Sciences* 1 (PUBMED).

¹⁹⁰Kefauver and Harris Amendments to *Federal Food, Drug and Cosmetic Act* 21U.S.C. § 301 (1938) for Canada see *Curran, supra* note 51.

¹⁹¹L. M. Friedman, C. D. Furberg & D. L. DeMets, *Fundamentals of Clinical Trials*, 3rd ed., (New York, Springer-Verlag, 1998) at 2 [Friedman].

¹⁹²See *FDAR, supra* note 71 at Division 5 - Definitions see also Canada, Government of Nova Scotia, Capital Health, *Research Manual: Policy & Procedure*, (Halifax: Capital Health, 2004), online: <<http://policy.cdha.ns.health.ca>>, accessed on June 12, 2006

There are a variety of different methods for completing a clinical trial, but well designed research shares certain qualities. As Stuart Pocock suggests:

The essence of a good clinical trial is that it provides truthful and precise information which is relevant to the treatment of future patients.... Methods of greatest value must be simple, reliable and readily understood by non-statisticians.¹⁹³

In formulating a clinical trial, a researcher must consider a host of factors, including but not limited to:

- (i) A written protocol
- (ii) Controlled trials
- (iii) Randomization
- (iv) Size of trial
- (v) Double blind trials
- (vi) Definition of patients
- (vii) Definition of treatments
- (viii) End-point evaluation
- (ix) Crossover trials
- (x) Forms and data management
- (xi) Statistical analysis
- (xii) Protocols
- (xiii) Monitoring of trial progress
- (xiv) Ethical considerations
- (xv) Multicentre trials
- (xvi) Staff, responsibilities and funding
- (xvii) Publication
- (xviii) Truth and relevance¹⁹⁴

The extent to which a clinical trial considers and addresses these requirements is generally a measure of the quality of the study's design and the value of the conclusions that can be drawn from its observations.

¹⁹³S. J. Pocock, "Statistical Aspects of Clinical Trial Design" (1982) 31(1) *The Statistician* 1 [Pocock].

¹⁹⁴*Ibid.* at 3.

(e) *Randomized Control Trials*

The most common form of clinical research used for the evaluation of new drugs is the Randomized Control Trial (RCT). The RCT has been defined as a:

carefully and ethically designed experiment which includes the provision of adequate and appropriate controls, by a process of randomization so that precise framed questions can be answered.¹⁹⁵

The RCT is seen as a good measure of a drug's efficacy since it enables comparisons of a drug's effect with other treatments. It is beyond the scope of this thesis to go into great detail cataloguing the variety of different methodologies employed in drug trials (i.e. case studies, longitudinal studies, comparison group studies),¹⁹⁶ but it will be useful to review some of the elements of a methodologically sound RCT. Before discussing these elements, it is essential to acknowledge that the best designed RCT usually focuses on testing "one major objective".¹⁹⁷ As Pocock notes:

Of paramount importance is the need for a good idea for potential improvement in therapy and to be able to achieve an honest and accurate evaluation of its real worth.¹⁹⁸

The RCT has at least three essential elements of design: randomization, blinding, and operational variables.

¹⁹⁵C. J. BulPitt, *Randomized Controlled Clinical Trials*, (Boston: Martinus Nijhoff Publishers, 1983) at 1 [Bulpitt].

¹⁹⁶For a comprehensive description of the varied methods in drug research and the conduct of clinical trials, see L. Gross-Portney & M. P. Watkins, *Foundations of Clinical Research: Applications to Practice*, (Norwalk, Connecticut: Appleton & Lange, 1993) [Portney], D. M. Murray, *Design and Analysis of Group-Randomized Trials*, (New York: Oxford University Press, 1998) [Murray] & S. C. Chow & J. Liu, *Design and Analysis of Clinical Trials: Concepts and Methodologies*, (Toronto: John Wiley & Sons, 1998) [Chow]. Some of these techniques include studies of mechanisms in human disease, studies of the management of disease, in vitro studies on material of human origin, animal models of human health or disease, field/observation surveys, quality-control of new diagnostic and therapeutic techniques, and assessment of health care delivery are a few, as reported in E. H. Ahrens, *The Crisis in Clinical Research: Overcoming Institutional Obstacles*, (New York: Oxford University Press, 1992) [Ahrens].

¹⁹⁷Bulpitt, *supra* note 195 at 28.

¹⁹⁸Pocock, *supra* note 193 at 3.

(i) Randomization

In an RCT treatment is allocated to participants by random (chance) procedure¹⁹⁹. To ensure accurate results, researchers must limit the bias that might result from assigning participants unequally to treatments. Randomization can avoid “subjective assignment of patients who participate in clinical trials [or limit] inequalities [in characteristics] between treatment groups (e.g. demographic details or prognostic variables)”²⁰⁰. As Friedman notes:

Randomization tends to produce study groups comparable with respect to known and unknown risk factors, removes investigator bias in the allocation of participants, and guarantees that statistical tests will have valid significance levels.²⁰¹

Randomization is based on the concept that “no judgmental or systematic bias should affect the way that patients are assigned to treatment”²⁰². It is based on the concept of appropriate population sampling, where study groups are expected to encapsulate as accurately as possible those variations which are found in the public (or a subpopulation) at large.²⁰³

(ii) Blinding

Normally an RCT should be conducted as a double-blind procedure. This means that neither participants nor researchers are aware of the treatments that participants are

¹⁹⁹*Chow, supra* note 196 at 122

²⁰⁰*Ibid.*

²⁰¹*Friedman, supra* note 191 at 61.

²⁰²*Pocock, supra* note 193 at 4.

²⁰³*Chow, supra* note 196 and *ibid.* at 152.

receiving. This is done to reduce the “bias caused by subjective judgements in reporting, evaluation, data processing and statistical analysis due to the knowledge of the identity of the treatments”.²⁰⁴ The expectation that a treatment will work can influence whether it is perceived to be working by both researchers and participants. Allowing participants to know that they are on a placebo or new treatment may affect their perception of its efficacy and change measured behaviours. For some trials, such as in the case of treating terminally ill patients, random assignment would not be ethical, and double blinding of treatment not possible. In these instances, it may be possible to partially blind the study by limiting the knowledge of researchers or those making clinical observations as to the treatments assigned.

(iii) Controls

Tested control groups should be “sufficiently similar in relevant respects to the intervention group so that differences in outcomes may reasonably be attributed to the action of the intervention”.²⁰⁵ This control enables comparisons of the known to the unknown and provides a “well-defined point, which becomes the zero or baseline of the study”.²⁰⁶ It is only by including such control measures that observations can be made to determine whether a treatment is better or equal to other treatments. For new drugs, ideally such clinical testing should be against proven existing treatments; it is in this way only that we can say new drugs are better than existing ones. Unfortunately, many

²⁰⁴*Ibid.* at page 152.

²⁰⁵*Friedman, supra* note 191 at 2

²⁰⁶*Ibid.* at 82.

clinical trials will use only a placebo (no treatment) as the control group, proving that new drugs are only better than “no treatment at all”.²⁰⁷

(iv) Measurable Variables or End Point Variables

In order to determine the usefulness of a treatment it must be measured. This is done by identifying “properties that can differentiate members of a group or set”²⁰⁸ and observing how these change by varying treatment. Independent variables (IV) are manipulated by the experimenters through assignment of participants to different drug groups and dependent variables (DV) are measured for signs of change. When measuring the outcome of treatment on behaviour, physiology, or illness, it is often difficult to directly assign them a value. In these cases, a secondary measure, an end point or clinical surrogate measure will often be used. These observations can either be qualitative (based on observation of qualities) or quantitative (based on some measurable amount) and must be defined before the study begins.²⁰⁹ End points can be a wide variety of measures which are taken as indicators of a drug’s effect (e.g., mobility for arthritis, blood levels of certain hormones, or even changes in morbidity).

²⁰⁷*TCPS*, *supra* note 69 which does place limits on the use of placebos where useful and existing therapies exist. There is extensive literature on the debate between placebo and active controls; see R. Temple & S. S. Ellenberg, “Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments” (2000) 133(6) *Annals of Internal Medicine* 455 (PUBMED) and S. Garattini, V. Bertele & L. LiBassi, “How Can Research Ethics Committees Protect Patients Better?” (2003) 326 *BMJ* at 1201 [Garattini].

²⁰⁸*Portney*, *supra* note 196 at 89.

²⁰⁹*See Murray*, *supra* note 196.

(f) A Note on Hypothesis Testing and Valid Sampling

Ignoring ethical considerations for the moment, there are at least two other qualities that characterize good clinical drug research that I would like to introduce: the formulation of a valid hypothesis (using valid research questions) and accurate sampling. Conducting worthwhile research means asking useful and purposeful questions. As one author suggests:

In a concise format, the research question specifies which factors or behaviors will be examined and what types of data will be collected.... they must be defined objectively, so that their meaning within the context of the study is clear....[the] hypothesis suggests how the variables are expected to be related. This hypothesis guides the investigation and subsequent analysis of data.²¹⁰

The hypothesis and intended analysis must be defined before the commencement of the study qualitative or exploratory research may supplement the refinement of data.²¹¹ As

Anderson notes:

the classifications of research projects into hypothesis testing and hypothetico-deductive is of crucial importance in evaluating the reliability of conclusions....medical investigators need to be warned against re-use of observations. Whenever data through inductive reasoning have been used to propose a hypothesis, new and independent observations are necessary to test it. If data through statistical analyses are re-used to test the very hypothesis which they served to generate, circularity and erroneous conclusions may result.²¹²

Science requires this form of inferential hypotheses testing; merely tailoring interpretation after the fact does not meet a basic threshold for inductive scientific

²¹⁰Portney, *supra* note 196 at 89.

²¹¹Friedman, *supra* note 191.

²¹²B. Anderson, *Methodological Errors in Medical Research*, (Cambridge: Massachusetts: Blackwell Scientific Publications, 1990) at 72 [Anderson].

reasoning.²¹³ Even worse, conducting research which addresses no hypothesis, or is so methodologically flawed that it generates a predetermined result, is pointless and needlessly puts the health of test subjects at risk.²¹⁴

Valid sampling can best be conceived as ensuring that the subjects being observed approximate those in the real world. As Portney notes, “an important goal of clinical research is to make generalizations beyond the individuals studied to others with similar conditions or characteristics”.²¹⁵ Every experiment is “based on limited experience and measurements”²¹⁶ so it can only generalize its conclusion to the real world. The greater extent to which subjects are drawn from diverse and representative populations who will consume a drug, the more accurate the conclusions drawn regarding that drug’s efficacy in a given population.²¹⁷ Testing an arthritis medication on healthy young volunteers does not approximate the vast majority of those who will ultimately use the product.²¹⁸ Sampling is also affected greatly by the size of a representative sample that is observed, the general rule being, the larger the sample the better it approximates the actual population.²¹⁹

²¹³See *Popper, supra* note 2.

²¹⁴*Chow, supra* note 196.

²¹⁵*Portney, supra* note 196 at 111.

²¹⁶*Ibid.*

²¹⁷*Chow, supra* note 196.

²¹⁸*Vioxx Lessons, supra* note 20.

²¹⁹*Chow, supra* note 196.

(g) A Note on Ethical Refinement of Research

At this time I would like to caution the reader that the above described methodologies do not operate in an ethical vacuum. All of the approaches described above need to be modified if they are likely to produce undue harm for participants.²²⁰ Justifying a Phase I TeG trial merely because it stops a dangerous product from reaching the larger public does not validate the harm done. Instead, it hints to the need for refinement of elements in the research's design, perhaps by incremental testing.²²¹ Likewise, randomization, blinding, end points, and tested hypotheses may also need to be adjusted to meet ethical considerations. Randomization will often need to be modified if over the course of a trial it is observed that some treatments represent vastly inferior or superior treatments, or induce irreversible harm.²²² Blinding may not be practical if it unduly places psychological or emotional distress on research participants, improper consent is not obtained or explained, or a serious adverse event is observed. End point measures need to take into account the health of participants and be as minimally intrusive as possible; using morbidity as an end point is not always acceptable.

²²⁰See E. J. Emanuel, R. A. Crouch, J. D. Arras, J. D. Moreno & C. Grady eds., *Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary*, (Baltimore: The Johns Hopkins University Press, 2003) [Emanuel] and A. E. Shamoo & D. B. Resnik, *Responsible Conduct of Research* (New York: Oxford University Press, 2003) [Shamoo].

²²¹*Goodyear, supra* note 161.

²²²A. Hellman & D. S. Hellman, "Of Mice and Men: Problems of the Randomized Control Trial" in *Emanuel, supra* note 220 at 113.

(h) Sources of Research Bias

Even with these tools of research available, there are still a host of methodological errors that can occur during clinical research. Researchers must be ever vigilant against bias in the generation of research models. Bias can basically be explained as “any effect at any stage of investigation or inference tending to produce results that depart systematically from the true values”.²²³ It is any factor which “deprives a result of representative [accuracy] through systematic distortion”.²²⁴ Bias can be both positive and negative (favouring or hindering the proof of a certain hypothesis) and skewing observation toward specific conclusions. In designing a clinical trial, researchers must develop a strategy for each study’s particular design to limit bias. As Murray notes:

The investigator must look at each study carefully, consider which potential sources of bias might apply, and then develop strategies to defend against those sources in the context of their study.²²⁵

Generally the tools described above are designed to limit the occurrence of bias, but if they are not appropriately and conscientiously employed they lead to poor research.

(i) Common Sources of Research Error

There are several common errors that may occur during clinical research.²²⁶ I have already mentioned sampling errors and hypothesis testing above. Subjects must be

²²³ Anderson, *supra* note 212.

²²⁴ *Ibid.*

²²⁵ Murray, *supra* note 196 at 23.

²²⁶ *Ibid.* at 23-63.

recruited to represent the populations who will receive a treatment. Hypotheses must be defined and executed by predetermined rules, as one author notes:

If even the briefest glance at a study's results moves the investigator to consider a hypothesis not formulated before the study was started, that glance destroys the probability of the evidence at hand.²²⁷

Researchers must be careful in selecting variables (end points indicating therapeutic change) beyond one-time or limited measures, and not assume that significant statistical changes always equate significant biological or therapeutic changes.²²⁸ Researchers must ensure that if end point measures are qualitative (observational), then there is uniformity among researchers taking the measurements.²²⁹ Beyond randomized assignment, researchers must be careful to avoid any other factors (historical, demographic, maturational) that might link participants in ways not controlled for by the study.²³⁰

There is also a host of more intentional errors that researchers may induce by favouring certain approaches to clinical research. As one author has noted:

Several kinds of widely accepted practices should be recognized as potentially deceptive and harmful. Some of these practices also have much value, but at times they are inappropriate and improper and, to the extent that they are deceptive, unethical.²³¹

Researchers have identified a wide number of errors that seem to plague drug research.²³² Drug studies may compare different treatments (drugs) at varying doses that are not truly equivalent.²³³ They may conduct research over time frames that are not long enough to

²²⁷J. C. Bailar, "Science, Statistics, and Deception" in *Emanuel*, *supra* note 220 at 395, [Bailar].

²²⁸*Bulpitt*, *supra* note 195 at 29.

²²⁹*Ibid.*

²³⁰See *Murray*, *supra* note 196 at

²³¹*Bailar*, *supra* note 227 at 396.

²³²See *Abramson*, *supra* note 23 at 101 -148.

²³³*Ibid.*

observe anything but short-term effects.²³⁴ They may abort research mid-trial that looks as if it is going to disprove a desired hypothesis, while sponsoring those experiments which seem to support a desired hypothesis. Researchers may analyze and report only that data which supports their hypothesis, or test only for certain variables (e.g. not doing liver tests in the Olivieri-Apotex study meant they would not find evidence of liver fibrosis).²³⁵

(j) Error in the Data used in the Approval Process

One could argue that poor methodological research is not occurring in those studies that the TPD uses for approval; but because the approval process and industry-submitted data is not generally available for scrutiny, the truth is that we simply do not know. In 2002, via a freedom of information request, the CBC obtained the research data upon which the withdrawn drug Diane-35 had originally received Health Canada approval.²³⁶ In reviewing this data, Barbra Mintzes observed:

Health Canada approved Diane-35 although it was not tested in the patient population it was approved to treat. Nor was it tested against a placebo on any other [comparable] treatments. Thus studies submitted ... did not establish Diane-35's effectiveness for its approved use.²³⁷

Of the five studies submitted for approval, only three were double blinded and two were open label. Of the open label studies, one was merely observational of a group of

²³⁴*Ibid.*

²³⁵See D. G. Nathan & D. J. Weatherall, "Academic Freedom in Clinical Research" (2002) 347 *NEJM* 1368 (PUBMED).

²³⁶CBC Market Place, "A Hard Pill to Swallow" *Canadian Broadcasting Corporation News* (20 March 2005), online: CBC <<http://www.cbc.ca/marketplace/pre-2007/files/health/diane/index.html>>.

²³⁷*Mintzes, supra* note 141 at 6.

patients on the drug, while the other was an RCT without blinding procedures. Of the three studies conducted using double-blind procedures, two compared Diane to a control group at an incomparable dose, while the third compared it to a contraceptive drug (not the use for which it was seeking approval). None of these three trials included a placebo group, tested the treatment on a group comparable to one whom the medication was intended for, or reported outcomes for patients who withdrew early (12%-33%).²³⁸ All of these methodological flaws weaken the conclusions that could be drawn about the drug's safety and efficacy.

In 1966, JAMA ran a simple experiment. Drawing 149 articles from the most respected medical journals, it asked statisticians to review the studies based on whether “the conclusions drawn were valid in terms of the design of the experiment, the type of analysis performed, and the applicability of the statistical tests used”.²³⁹ Only 44 studies passed (28%).²⁴⁰ A similar study conducted 20 years later found the same result, with only 24% of the studies surveyed passing.²⁴¹ A similar study a decade later found that only 6.8% met criteria for robust research methodology.²⁴²

Trying to limit this error is one of the essential elements of conducting ethical and worthwhile research. As one author notes:

²³⁸*Ibid.* at 5.

²³⁹S. Schor & I. Karten, “Statistical Evaluation of Medical Journal Manuscripts” (1966) 195(6) *JAMA* 1123.

²⁴⁰*Ibid.*

²⁴¹P. C. Götzsche, “Methodology and Overt and Hidden Bias in Reports of 196 Double-Blinded Trials of Nonsteroidal, Anti-inflammatory Drugs in Rheumatoid Arthritis” (1989) 10 *Control Clin. Trials* 31.

²⁴²J. G. Lijmer, B. W. Mol, S. Heisterkamp, G. J. Bonsel, M. H. Prins, H. H. P. VanderMeulen & P. M. M. Bossuyt, “Empirical Evidence of Design-Related Bias in Studies Assessing Diagnostic Tests” (1999) 282 *JAMA* 1061 for a more recent study see A. W. S. Rutjes, J. B. Retisma, M. DiNisis, N. Smidt, J. C. VanRijn & P. M. M. Bossuyt, “Evidence of Bias and Variation in Diagnostic Accuracy Studies” (2006) 174(4) *CMAJ* Online (PUBMED).

No amount of statistical analysis or interpretation can overcome a design flaw, data that results from flawed design are virtually useless, and using them can be unethical. Obtaining useless data wastes time, money, and effort and it can also involve the unnecessary use of human or animal subjects.²⁴³

Just as problematic is the effect that poor research may have on treatment practice and decisions about whether a drug should be available to the consuming public. As Anderson suggests, “with methodologically flawed studies there is always the risk that conclusions will not hold for future patients”.²⁴⁴ To the extent that approval decisions are based on this flawed methodology, they cannot effectively be predictive of a drug’s safety when released to the public. Without robust scientific inquiry backing up decisions related to risk, these decisions become meaningless.

The Law and the Regulation of the Clinical Trial

While we cannot assess the criteria and science that the TPD applies to the data it receives with an NDS, we can look back in the process at the point where rules are applied in governing clinical trials. Having established some of the criteria of good research design, we can now look at those legal standards imposed on researchers to meet these criteria in designing and implementing drug research in Canada. There is the potential that if these rules are weak, they will allow for the creation of poor quality research. The result would be the production of research studies for the approval process that are not methodologically sound and are poorly indicative of a drug’s safety or efficacy.

²⁴³Shamoo, *supra* note 220 at 43.

²⁴⁴Anderson, *supra* note 212 at 8.

As noted in Chapter 1, there are several legal instruments that guide the design and administration of clinical research in Canada (i.e. the FDA, FDAR, TCPS, *ICH Guidelines*, and *Declaration of Helsinki*). A host of institutional and a few provincial regulations and guidelines are also in operation²⁴⁵ as well as some international guidelines.²⁴⁶ Two basic sentiments drawn from the *Declaration of Helsinki* underlie much of this guidance:

Section 5. In medical research on human subjects, *considerations related to the well being of the human subject should take precedence over the interests of science and society.*

Section 11. Medical research involving human subjects *must conform to generally accepted scientific principles*, be based on a thorough knowledge of the scientific literature, other relevant sources of information and on adequate laboratory and, where appropriate, animal experimentation.²⁴⁷

Section 5 implies that research cannot be justified when it abrogates the right of subjects simply to meet the demands of science or society. Section 6 asks researchers to be informed and design research that “conforms to generally accepted scientific principles”.²⁴⁸ The concepts that human subject rights are paramount and that research must meet current standards of scientific convention are essential to the integrity and value of drug research.

²⁴⁵See Health Canada, *Clinical Trial Applications* (Ottawa: Health Canada, 2009), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.php>.

²⁴⁶*Ibid.*

²⁴⁷*Helsinki*, *supra* note 65.

²⁴⁸*Ibid.*

(a) Statutory Authority to Legislate Clinical Trials

Parliament does not directly indicate that testing of new drugs is required in the body of the FDA. Instead it restricts the right to market the product unless certain conditions are met. Under section 9 of the *Food and Drug Act* it is prohibited to:

label, package, treat, process, sell or advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety.²⁴⁹

Determining the nature of a drug requires some form of objective testing as to its “character, value, quantity, composition, merit or safety”.²⁵⁰ Character (chemical qualities), quantity, and composition of a drug will be determined by toxicology and quality studies that are submitted with an NDS. Character (medicinal), value, merit, and safety will be met by the submission of studies that prove the therapeutic worth (e.g., safety and efficacy) of the drug.

The FDA method for ensuring compliance is to limit market access for drugs unless certain standards are met. Under section 10(1) of the FDA:

Where a standard has been prescribed for a drug, no person shall label, package, sell or advertise any substance....unless the substance complies with the prescribed standard.²⁵¹

In establishing this standard under s.30, the Governor in Council gives broad powers to make regulations respecting the “sale or conditions of sale of any food, drug, cosmetic or device”.²⁵² It specifically allows for the setting of regulations related to “the sale or the

²⁴⁹*FDA, supra* note 89 at s. 9.

²⁵⁰*FDAR, supra* note 71.

²⁵¹*FDA, supra* note 89 at s. 10(1).

²⁵²*Ibid.*, s. 30(1)(b)(iii).

conditions of sale of any new drug”.²⁵³ This includes regulation to prevent the public (purchaser or consumer) from:

being deceived or misled in respect of the design, construction, performance, intended use, quantity, character, value, composition, merit or safety thereof, or to prevent injury to the health of the purchaser or consumer.²⁵⁴

Under s. 30(1) (1.1) this also includes regulations:

respecting the assessment of the effect on the environment or on human life and health of the release into the environment of any food, drug, cosmetic or device, and the measures to take before importing or selling such [product].²⁵⁵

(b) The Food and Drug Regulations

From these provisions flow the *Food and Drug Regulations*. Division 5 of the *Food and Drug Regulations (Drugs for Clinical Trials Involving Human Subjects)* provides the following three key features:

- (ci) Clear and transparent requirements of application, information, amendments, notification, labelling, record keeping and adverse drug reaction reporting
- (cii) Introduction of an inspection system against internationally accepted good clinical practice principles, and
- (ciii) Give clear authority to refuse an application, suspend or cancel the sale of drugs for use in clinical trials...where they do not met the updated regulatory requirements.²⁵⁶

The FDAR’s main mode of action was to “introduce regulatory requirements for the *sale and importation* of drugs for use in human clinical trials”.²⁵⁷

²⁵³*Ibid.*, s. 30(i)(o)(ii).

²⁵⁴*Ibid.*, s. 30(1)(b)(iv).

²⁵⁵*Ibid.*, s. 30(1)(1.1).

²⁵⁶*Ibid.*, at the Regulatory Impact Analysis.

²⁵⁷*Ibid.*

(c) The Clinical Trial Application

Before a clinical trial can commence for a drug not approved for use in Canada, the trial's sponsor²⁵⁸ must file a Clinical Trial Application (CTA).²⁵⁹ The CTA is a request for an "authorization to sell or import a drug for the purposes of a clinical trial" and must include:

- (a) A copy of the protocol for the clinical trial
- (b) A copy of the informed consent form that will be given to participants
- (c) The clinical trial attestation
- (d) The name and contact information of any REB that has previously refused to sanction the study
- (e) A copy of the investigator's brochure
- (f) Proposed date for the commencement of the trial.²⁶⁰

The details of what is to be included within the CTA are elaborated in the policy document *Guidance for Clinical Trial Sponsors: Clinical Trial Applications*,²⁶¹ which more clearly identifies administrative and clinical information, chemistry and manufacturing details, and quality data that must be submitted. The Minister or his/her designate has 30 days to reject the application if:

- (i) the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person
- (ii) the clinical trial is contrary to the best interests of a clinical trial subject, or
- (iii) the objectives of the clinical trial will not be achieved²⁶²

²⁵⁸Sponsor is defined as "an individual, corporate body, institution or organization that conducts a clinical trial," *FDAR*, *supra* note 71 at s. C.05.001.

²⁵⁹*Ibid.*, s. C.05.006.

²⁶⁰*Ibid.*, s. C.05.005

²⁶¹Health Canada, *Guidance for Clinical Trial Sponsors: Clinical Trial Applications* (Ottawa: Ontario, 2003), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/ctabio_decbio_e.html>, accessed on October 12, 2005 [Guidance CT].

²⁶²*FDAR*, *supra* note 71 at s. C.05.006.

(i) Investigator's Brochure

The investigator's brochure is a description of the information obtained regarding a drug to date, or "a document containing the pre-clinical and clinical data on the drug".²⁶³ This will include: physical and chemical properties of the drug, pharmacological aspects from animal testing, pharmacokinetic properties from animal testing, toxicological effects from animal testing, carcinogenicity from animal testing, and information obtained from previous clinical trials (safety, efficacy, dose response, etc.). The brochure is intended to provide all pre-clinical tests (including animal tests and chemical tests) and details of previously conducted clinical trials.

(ii) Clinical Trial Attestation

The clinical trial attestation provides administrative details regarding the drug and execution of the clinical trial. These details include: title of the protocol, chemical and brand names of the drug, therapeutic classification of the drug, medicinal ingredients of the drug, dosage form, contact information for the sponsor (or Canadian representatives), contact information for qualified investigators, contact information for REBs which have given the study approval, and a statement from the sponsor. The qualified investigator (QI), normally a physician or dentist, is:

the person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the law of the province where the clinical trial site is located.²⁶⁴

²⁶³*Ibid.*, s. C.05.001 and *Guidance CT*, *supra* note 261.

²⁶⁴*Ibid.*, s. C.05.001

The attestation statement includes undertakings that “the clinical trial will be conducted in accordance with good clinical practices“.²⁶⁵

(iii) The Protocol

The protocol is a description of the study’s scientific rationale and intended organization. The Act defines a protocol as “a document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial”.²⁶⁶

A protocol is described in the medical literature as:

a plan that details how a clinical trial is to be carried out and how data are to be collected and analyzed. It is an extremely critical and most important document, since it ensures the quality and integrity of the clinical investigation in terms of its planning, execution, and conduct of the trial as well as analysis of the data.²⁶⁷

It is intended to be a description of the research hypothesis, variables (measures), design and methods, results analysis, and administrative details of the trial. As Friedman suggests, it can be considered “as a written agreement between the investigator, the participant, and the scientific community”.²⁶⁸

²⁶⁵*Guidance CT, supra* note 261

²⁶⁶*Ibid.*, s. C.05.001.

²⁶⁷*Chow, supra* note 196 at 19.

²⁶⁸*Friedman, supra* note 191 at 10.

(d) Good Clinical Practices

The FDAR requires that clinical trials are completed “in accordance with *good clinical practices* (GCP)”.²⁶⁹ The Act defines good clinical practices as:

generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons, and the good clinical practices referred to in section C.05.010.²⁷⁰

In defining appropriate methodology, section C.05.010 merely requires that the “trial is scientifically sound and clearly described in a protocol”²⁷¹ and conducted in accordance with the protocol. Section C.05.010 provides some guidance as to what these acceptable clinical practices must include. It requires written informed consent, protection of records, REB approval, and good manufacturing and handling procedures.²⁷² It also requires that “medical care and medical decisions”²⁷³ are made by a qualified investigator and that “each individual involved in the conduct of the trial is qualified by education, training and experience to perform his or her task”.²⁷⁴

(e) Scientifically Sound and the Provision of a Protocol

Defining something as scientifically sound does not ensure that the best or even appropriate methodology is employed. Instead it allows for a wide collection of accepted practices that may or may not be scientifically robust. Many studies can be

²⁶⁹FDAR, *supra* note 71. at C.05.010.

²⁷⁰*Ibid.*, s. C.05.001.

²⁷¹*Ibid.*, s. C.05.010(a)(b)

²⁷²*Ibid.*, s. C.05.010(h)(i)(d) & (j) respectively.

²⁷³*Ibid.*, s. C05.010(f).

²⁷⁴*Ibid.*, s. C.05.010(g).

argued as sound, without taking into account the fact that the quality of clinical trials can vary substantially. What is to be included in a protocol is delineated by Health Canada in the *Pre-Clinical and Evaluation Report Template* (PCERT). Also known as the *protocol synopsis*, the main thrust of this document is “a submission rationale and a brief summary”²⁷⁵ of the study’s design and administration. The protocol must identify such topics as trial objectives, study design, list of investigators, statistical analysis, but does not require that sponsors demonstrate they have chosen those criteria that are most likely to minimize bias and errors.

The main thrust of the contents of the protocol is the identification of a justifiable methodology, rather than adherence to the most sound or accurate methodologies in research design.²⁷⁶ Sponsors are asked to demonstrate that the “design of the study should be able to support any claims related to the proposed study”.²⁷⁷ This includes “the method of randomization, blinding, and the comparative agents, if applicable”.²⁷⁸ It also includes identifying a sample size to be used, patient populations, inclusion/exclusion criteria and efficacy variables (end points), but asks for little more than a “description and validation”²⁷⁹ of selected criteria. Studies may appear to contain all the properties and elements of a good protocol and still be “tainted by dubious premises, invalid designs, unreliable data, violated assumptions, bias, erroneous methods or faulty reasoning.... [and] faulty logic”.²⁸⁰

²⁷⁵See *Guidance CT*, *supra* note 261 at appendix 4.

²⁷⁶It should be noted that the most sound and accurate methodologies may be varied for ethical cases, but this is not automatically the case; see *Garattini*, *supra* note 207.

²⁷⁷*Guidance CT*, *supra* note 261 at 36.

²⁷⁸*Ibid.*

²⁷⁹*Ibid.* at 38

²⁸⁰*Friedman*, *supra* note 191 at vii.

(f) *Study Protocol, Good Clinical Practices and the ICH Guidelines*

(i) *ICH Guidelines*

Instead of specifying which methodologies are most appropriate for researchers, Health Canada directs sponsors to the *International Conference on Harmonization (ICH) Guidelines* to:

define parameters of the design, conduct, performance, monitoring, auditing, recording analysis, and reporting of clinical trials [as a set of] recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration.²⁸¹

There are three sections of the ICH guidelines which bear directly on the appropriate methods that should be employed in clinical trials: *ICH Topic E6: Good Clinical Practices*,²⁸² *ICH Topic E8: General Considerations for Clinical Trials*,²⁸³ and *ICH Topic E9: Statistical Principles for Clinical Trials*.²⁸⁴

The ICH guidelines are not law. Instead, they have been ‘adopted’ by Health Canada but are not formally incorporated into statute or regulations. They are guidance documents meant to:

²⁸¹International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Objectives of the ICH*, online: <<http://www.ich.org>>, accessed on March 6, 2006.

²⁸²Health Canada, *Guidance for Industry: Good Clinical Practices - Consolidated Guideline ICH Topic E6* (Ottawa: Health Canada, 1997), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6_e.html> [ICH E6], accessed in October 12, 2005.

²⁸³Health Canada, *Guidance for Industry: General Considerations for Clinical Trials ICH Topic E8* (Ottawa: Health Canada, 1997), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e8_e.html> [ICH E8], accessed on October 12, 2005.

²⁸⁴Health Canada, *Guidance for Industry: Statistical Principles for Clinical Trials ICH Topic E9* (Ottawa: Health Canada, 2003), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e9_e.html> [ICH E9], accessed on October 12, 2005.

Provide assistance to industry and health care professionals on how to comply with the policies and governing statutes and regulation. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.²⁸⁵

As noted in the foreword to the ICH guidelines provided by Health Canada:

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. *Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification.*²⁸⁶

In effect the ICH guidelines are merely suggested practices that industry should adopt.

While investigators may be reviewed for compliance against these standards by the Health Products and Food Branch Inspectorate (HPFBI), the ICH guidelines must be followed only to the extent that ‘adequate scientific justification’ cannot allow different standards.

(ii) Defining Good Clinical Practices in the ICH Guidelines

The ICH guidelines provide a more detailed description of what is considered good clinical practice. According to ICH E6, good clinical practices can be described as:

A standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.²⁸⁷

Good clinical practices within the ICH have two components: (1) measures to assure that the design of a study produces valuable data, and (2) measures to protect the rights

²⁸⁵ ICH E6, *supra* note 282.

²⁸⁶ *Ibid.*

²⁸⁷ *Ibid.* at 1.24

of study participants. In formulating study design, researchers are reminded that the “integrity of the trial and the credibility of the data from the trial depend substantially on the trial design”.²⁸⁸ As such, in designing a study, researchers should provide detailed ‘descriptions’ of methods used to minimize or avoid bias, type or design of trial to be conducted, descriptions of trial treatments, duration of treatments, inclusion/exclusion criteria, assessments of efficacy and safety, and statistical methods to be employed.

(iii) ICH Topic E8: General Considerations for Clinical Trials

ICH Topic E8 provides more specific detail about what should be included in the completion of good clinical trials. It suggests that several “important principles should be followed in planning the objectives, design, conduct, analysis and reporting of a clinical trial”.²⁸⁹ Underlying these principles is a valid scientific approach in design and analysis of studies, where:

Clinical trials should be designed, *conducted and analyzed according to sound scientific principles to achieve their objectives*; and should be reported appropriately. The essence of rational drug development is to ask important questions and answer them with appropriate studies.²⁹⁰

ICH E8 asks that “the appropriate design should be chosen to provide desired information”.²⁹¹ It also provides more detailed considerations to be employed to ensure accurate results. Subjects should be selected to represent target patient populations

²⁸⁸*Ibid.* at 6.4.

²⁸⁹*ICH E8, supra* note 283.

²⁹⁰*Ibid.* at 2.2.

²⁹¹*Ibid.* at 3.2.2.

using selection criteria that are accurate.²⁹² In designing studies, there needs to be “an adequate control group...to minimize the likelihood of erroneous inference”.²⁹³

Selecting a sample size should account for the “the expected magnitude of the treatment, the variability of the data, and the specified probability of error”.²⁹⁴

Response variables (end points) “should be defined prospectively [and] objective methods of observation should be used”.²⁹⁵ These guidelines also specifically state that randomization and blinding are preferred methods for reducing bias.²⁹⁶

(iv) ICH Topic E9: Appropriate Statistical Principles

ICH Topic E9 is very specific in defining appropriate statistical measures to be incorporated into study design and analysis to ensure the statistical veracity of the study. It catalogues the variety of different designs possible and the statistical consideration that must be considered with each form of design and methodology. For instance, it notes that global assessment variables (investigators’ overall impressions) are ultimately subjective in nature and can “lead to the results of two products being declared equivalent despite having very different profiles of beneficial and adverse effects”.²⁹⁷ Similarly, E9 cautions that “redefinition of the primary variable after unbinding will almost always be unacceptable”.²⁹⁸ Yet in describing its scope and direction, E9 states:

²⁹²*Ibid.* at 3.2.2.1.

²⁹³*Ibid.* at 3.2.2.2.

²⁹⁴*Ibid.* at 3.2.2.3

²⁹⁵*Ibid.* at 3.2.2.4

²⁹⁶*Ibid.* at 3.2.2.5.

²⁹⁷*ICH E9, supra* note 284.

²⁹⁸*Ibid.*

The focus of guidance is on statistical principles. It does not address the use of specific statistical procedures or methods. Specific procedural steps to ensure that principles are implemented properly are the responsibility of the sponsor.²⁹⁹

E9 is not to be considered an endorsement or value judgment regarding various statistical methodologies that can possibly be employed; it simply provides a catalogue of considerations that must be addressed in formulating the trial. Accounting for the methods and design of the study, and the ‘procedural steps’ necessary, are still the responsibility and potential discretion of trial sponsors.

(v) The Protocol under the ICH guidelines

Under the ICH guidelines, the main method for ensuring that these methods are met is still the existence of a protocol. The ICH E6 suggests that a protocol “*usually gives the background and rationale for the trial*”.³⁰⁰ The ICH E6 also reinforces the requirement that “the investigator should conduct the trial in compliance with the protocol”,³⁰¹ and cautions that “the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol”.³⁰² The content of a protocol should reflect those considerations which will ultimately appear in the *Clinical Study Report* provided with a new drug submission.

This report should draw on the study’s original protocol to provide:

a clear explanation of how the critical design features of the study were chosen and enough information on the plan, methods and conduct of the study so that there is no ambiguity in how the study was carried

²⁹⁹*Ibid.* at 1.2.

³⁰⁰*Ibid.* at 1.44.

³⁰¹*Ibid.* at 4.5.1.

³⁰²*Ibid.* at 4.5.3.

out...[enough] to allow replication of the critical analyses when authorities wish to do so.³⁰³

Again, researchers are given freedom in formulating the parameters under which methodological considerations are addressed. In discussing randomization procedures, ICH E6 indicates:

The investigator should follow the trial's randomization procedure, if any, and should ensure that the code is broken only in accordance with the protocol.³⁰⁴

Similarly, in defining the contents of a protocol, in section 6 the major requirement is that researchers provide a description of the methods employed.

(vi) The ICH Guidelines in Perspective

Given that the ICH guidelines are only 'guidance' which may be varied "provided they are supported by adequate scientific justification",³⁰⁵ it is difficult to judge the extent to which they ensure good study design. ICH Topics E6, E8, and E9 do suggest a series of 'considerations' that research must take into account in designing and implementing studies, but nowhere do these recommendations weigh the relative scientific merit of various trial designs or suggest the most appropriate forms of research. What they do is suggest once again that research should be conducted in accordance with good clinical practices. Good clinical practices in turn call for the adherence to a specified protocol and the protection of research participants. The

³⁰³Health Canada, *Guidance for Industry: Structure and Content of Clinical Study Reports ICH Topic E3*, (Ottawa: Health Canada: 1996), online: <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e3_e.pdf> [ICH E3], accessed on October 12, 2005.

³⁰⁴*Ibid.* at 4.7.

³⁰⁵*Ibid.*

protocol is a description of prospective research, justifying chosen criteria on existing scientific principles. As will be described, sound scientific principles may allow for the introduction of a wide collection of research which is weak yet maintains the appearance and norms of accurate research.

(g) Further Guidance from the Tri-Council Policy Statement (TCPS)?

A third document which may give guidance regarding the employment of appropriate methodologies in research is the *Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans* (TCPS).³⁰⁶ As noted in Chapter 1, the TCPS is a set of ethical guidelines that provide direction for “the conduct of research involving human subjects”.³⁰⁷ They are binding on any researcher or institution with researchers who receives grants from one of the major federal research funding bodies (CIHR, NSERC, or SSHRC).³⁰⁸ Organizations which do not receive funding from any of the councils, such as private Contract Research Organizations (CRO), may not be subject to the TCPS.

(i) A Patient-Centred Perspective

The TCPS is based on a “subject-centered perspective” that places an emphasis on “active involvement by research subjects, and ensuring that their interests are central

³⁰⁶TCPS, *supra* note 69 at i.7. The TCPS Policy Statement is preparing to release a new edition that should be published later in 2010.

³⁰⁷*Ibid.*

³⁰⁸*Ibid.*

to the project or study, and that they will not be treated simply as objects”.³⁰⁹ As such, the TCPS embodies such principles as respect for human dignity, respect for free and informed consent, respect for vulnerable persons, respect for privacy and confidentiality, respect for justice and inclusiveness, balancing harms and benefits, minimizing harm, and maximizing benefit.³¹⁰ In achieving these goals the TCPS introduces a host of procedural and administrative requirements placed upon researchers to protect the rights of the subject; these include obtaining free and informed consent, ensuring the privacy and confidentiality of patient records, including underrepresented populations in research, and minimizing conflicts of interest.³¹¹

As noted above, science cannot operate free of ethical restraint. Working hand in hand with sound statistical and methodological study design is the requirement that special consideration be given to participants when following standard research practices will cause undue harm. Research in emergency health situations should only be conducted “if it addresses the emergency needs of individuals involved”.³¹² Women are not to be excluded from research “solely on the basis of sex or reproductive capacity”.³¹³ Embodied in each of these concepts is the fact that “modern research ethics are premised on a dynamic relationship between ethical principles and procedures”.³¹⁴

³⁰⁹*Ibid.*

³¹⁰*Ibid.*

³¹¹*Ibid.*

³¹²*Ibid.* at Article 2.8.

³¹³*Ibid.* at Article 5.2.

³¹⁴*Ibid.* at i.9.

(ii) Clinical Equipoise and Accurate Study Design

The TCPS does acknowledge that changing research design for other reasons than ethical considerations is not easily justified. The TCPS calls on researchers to employ *clinical equipoise* in conducting research, requiring that:

...at the start of the trial, there must be a state of clinical equipoise regarding the merits of regimen to be tested, and the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully conducted, clinical equipoise will be disturbed.³¹⁵

The TCPS defines equipoise as:

...a genuine uncertainty on the part of the expert medical community about the comparative therapeutic merits of a clinical trial. The tenet of clinical equipoise provides a clear foundation to the requirement that the health care of subjects not be disadvantaged by research participation.³¹⁶

Equipoise reinforces the concept that research should not be conducted needlessly, without valid doubt as to outcome or without accurate methods in ascertaining one's hypothesis. Conducting research to produce desired outcomes by tailoring variables, or conducting research that does not take into account the scientific norms of medicine, likely violates clinical equipoise.

(iii) The TCPS and Administration of Trials

While the TCPS does provide detailed instructions for review of the ethical elements of a clinical trial, it does not provide direct instruction on trial

³¹⁵*Ibid.* at Article 7A.

³¹⁶*Ibid.*

methodology.³¹⁷ The thrust of the TCPS is in the details of how a trial should be administered and those protections that must be in place to ensure the safety, privacy, and consent of participants. The TCPS patient-centered perspective is focused mainly on protecting the rights of participants in research rather than ensuring the demonstrated scientific merit of research. The TCPS looks to REBs to ensure that the rights of research participants are not violated, to oversee the research merits of new studies, and to a lesser extent to assess the validity of research. Yet it is arguable that the quality and content of this research is less likely to be appraised than the administrative measures in place to protect participant rights.

(h) The Assessment of Sound Scientific Methodologies

(i) Qualified Investigators

We are left with the question, who is in fact reviewing the quality of clinical research conducted in Canada? The FDAR does require that research is overseen by a qualified investigator. A qualified investigator is defined in the FDAR as

The person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where the clinical trial site [is located]³¹⁸

The FDAR further suggests that “each individual involved in the conduct of the clinical trial should be qualified by education, training, and experience to perform his or her

³¹⁷It should be noted that the TCPS does discuss the need for clinical equipoise, or that “a state of clinical equipoise regarding the merits of the regimens to be tested” must exist, but this is equated with a scientific uncertainty regarding the outcomes of various treatments to be tested, not the merits of the methodologies employed. Articles 7.1-7.4 all discuss the need for ongoing ethics considerations and protection of participants throughout various types of trials.

³¹⁸FDAR, *supra* note 71 at C.05.001

respective tasks”.³¹⁹ Yet the qualified investigator is not in a position to oversee the study’s design; instead their role is to “assume responsibility for the proper conduct of the trial [and make] medical care and medical decisions”³²⁰ at the trial site; basically, to ensure the safety and health of the participants taking part in the trial. Their main role, as suggested in the ICH guidelines, is to ensure that the trial is completed “in compliance with the protocol agreed to by the sponsor”³²¹ and to monitor for adverse events.

Yet qualified investigators are often pressured to not be impartial. As was shown by the Nancy Olivieri case, there is potential for qualified investigators to be improperly pressured by trial sponsors.³²² In those situations where sponsors have a significant financial stake in research outcomes, pressure will exist³²³ on qualified investigators to generate studies that provide findings which reflect their interests. This may include ignoring flaws in methodology, adjusting observations during the course of a study, and even excluding data that runs contrary to desired conclusions. Even more problematic are the financial links that often exist between qualified investigators and sponsors. Many qualified investigators have direct or indirect links with industry

³¹⁹*Ibid.* at C.05.010(g).

³²⁰See *ICH 6*, *supra* note 282 at 6.

³²¹*Ibid.*

³²²See Canadian Association of University Teachers, *The Olivieri Report: The Complete Text of the Report of the Independent Inquiry Commissioned by the Canadian Association of University Teachers* (Toronto: James Lorimer & Company Ltd: 2001) & J. Downie, P. Baird & J. Thompson, “Industry and the Academy: Conflicts of Interest in Contemporary Health Research” (2002) 10 *Health L. J.* 103.

³²³For an excellent discussion of the pressures on researchers to generate industry positive data see R. DeVries & T. Lemmens, “The Social and Cultural Shaping of Medical Evidence: Case Studies from Pharmaceutical Research and Obstetric Science” (2005) 62(11) *Social Science & Medicine* 2694.

sponsors who pay for studies.³²⁴ As was noted in Chapter 2, such industry links can be problematic because they tend to:

redirect the orientation of research towards multiple ends, impede the sharing of research results, lead to early termination of trials, suppress or delay publication, produce publication bias that overemphasizes the positive aspects of drugs, and systematically yield results that favor the products being tested.³²⁵

In these situations, qualified investigators' motives, incentives, and impartiality can become questionable.

(ii) Health Canada

Health Canada has the capacity and expertise to review clinical trials, yet they have largely ceased to provide critical appraisals of trial design, and have come to focus on the existence of a protocol rather than sound design before approving a new clinical trial. Health Canada can provide a pre-CTA consultation meeting with trial sponsors in which they can “provide guidance on the acceptability of the proposed trial(s)”.³²⁶ Part of the CTA that they will review in advance includes sponsors’:

- (1) statement of trial design
- (2) parameters, values, ranges or limits for indication(s) and clinical use(s), patient study population(s) and routes of administration
- (3) parameters, values, ranges or limits for dosage form(s), dosage regimen(s) and formulation(s)
- (4) proposed procedures and/or criteria for patient monitoring, clinical efficacy and safety assessments, alternative treatments, premature patient discontinuation and other considerations, as appropriate.³²⁷

³²⁴*Ibid.*

³²⁵J. R. Lexchin, “Implications of Pharmaceutical Industry Funding on Clinical Research” (2005) 39 *The Annals of Pharmacotherapy* 194 (PUBMED) [Lexchin Implications].

³²⁶*Guidance CT*, *supra* note 261 at 4.1.

³²⁷*Ibid.* at 4.1(c) (i)-(iv).

This allows for a thorough review of a sponsor's design and protocol by experts at Health Canada before a clinical trial application is submitted.

Increasingly, however, Health Canada has started to conduct fewer pre-submission evaluations of clinical trial design. Health Canada has moved away from willingly assessing complete pre-clinical reports because of the volume of data to review.³²⁸ Instead the regulator must look retroactively at study design at the time of drug approval, and only at that data provided by manufacturers. Sound scientific research has come to be equated with justified research, defensible selection of methods, as articulated in an existing protocol. The protocol has come to be more a listing of accepted common practices rather than application or quality assessment of those practices.

(iii) Research Ethics Boards

According to the FADR, “for each clinical trial site, the sponsor [must] obtain the approval of the research ethics board in respect of the protocol”.³²⁹ Under the FDAR, an REB is a body “not affiliated with the sponsor”,³³⁰ whose:

principal mandate...is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being.³³¹

³²⁸See Health Canada, *Pre-Clinical Trail Application (CTA) Consultation Meetings* (Ottawa: Health Canada), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_pre_application-eng.php> and Health Canada, *Guidance for Clinical Trial Sponsors*, (Ottawa: Health Canada, 2003), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.php> [CT Guidance].

³²⁹*FDAR*, *supra* note 71 at s. C.05.006(c).

³³⁰*Ibid.*, s. C.05.001.

³³¹*Ibid.*

The composition of the REB is to include a range of experts in medicine, ethics, law, external disciplines, a community member, and:

two members whose primary experience and expertise are in a scientific discipline, who have broad experience in the methods and areas of research to be approved.³³²

The main thrust of this review is the rejection or approval of a researcher's (clinical-trial-qualified investigator's) protocol and consent materials. As part of this mandate, the REB will generally review the proposed study design as well as the safeguards in place to protect participants. Yet we are left asking how completely REBs assess the quality of research design.³³³

Unfortunately, REBs in effect become the main point at which study design is expected to be evaluated. We must ask how effective it is that a body chiefly charged with "safeguarding the rights, safety, and well-being of all trial subjects"³³⁴ is the primary body also evaluating the validity, soundness, and accuracy of study design. As the TCPS notes, "the review is undertaken in local research institutions by independent, multidisciplinary ethics committees that apply substantive and procedural norms".³³⁵

REBs are not in fact positioned to provide unbiased (or independent) reviews of study methodology. Often REBs do not have the expertise to assess methods nor the processes for getting external help with design methodology review.³³⁶ As Hadskis has

³³²*FDAR, supra* note 71. at s. C.05.001

³³³See *Hadskis, supra* note 100.

³³⁴*ICH E6, supra* note 282.

³³⁵*Hadskis, supra* note 100.

³³⁶*Ibid.* at 270.

noted, “the regulatory framework for human research is marred by complexity and inefficiency”.³³⁷ In fact, the extent to which an REB will exercise their responsibilities depends upon:

the particular country or countries, province or provinces, and institution or institutions that will host the research; the type of research being conducted; the professional and institutional affiliations of the researchers, the age and mental status of the participants; the type of information and material collected from or about participants and the funding sources for the research.³³⁸

This means that ultimately there is no uniform way in which REBs assess the scientific soundness of a protocol. There is even debate as to whether REBs should be assessing the scientific rigour or merit of study design or whether their main role is as a “consultative body on research ethics”.³³⁹

It does not suffice to ask REBs to fulfill the role of determining if clinical research design has sufficient validity. Ultimately the responsibility for ensuring good design must fall on the regulator and/or the manufacturer. The SEQ standard is only as good as the science that is provided to support it, demonstrating the value and safety of each new drug. This is only accomplished by ensuring the appropriate scientific standards are required by law and policy, or by monitoring more closely the quality of scientific methodology employed by drug manufacturers.

³³⁷*Ibid.* at 309.

³³⁸*Ibid.*

³³⁹*Ibid.*

CHAPTER 4: AN IMPROPER BALANCING OF CONCERNS

Introduction

For the past 20 years, the dominant theme of policy and regulatory activities for drug regulation has been limited to the safety, efficacy, and quality of the product, or the SEQ standard. Before a drug could be approved, it had to be demonstrated to be “safe, effective and of high quality”.³⁴⁰ Safety was assured by the prevention of human toxicity, efficacy was assured by the demonstration of the drug’s relative merit in treating conditions, and quality was assured by following the standards of good manufacturing practices.

The historical development of drug science and regulation has paralleled a recognition that each of these standards must be met: first, by imposing quality standards to prevent adulteration, secondly by imposing safety standards to ensure the safety of the product in humans, and finally by imposing efficacy standards to ensure the product’s utility or relative merit. Under the current *Food and Drug Regulations*³⁴¹ all new drugs must demonstrate:

- (e) details of the method of manufacture and the controls to be used in the manufacture, preparation and packaging of the new drug;
- (f) details of the tests to be applied to control the potency, purity, stability and safety of the new drug;
- (g) detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended;
- (h) substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended.³⁴²

³⁴⁰FDAR, *supra* note at 71 at C.08.002(2) (e)(f)(g)(h)

³⁴¹*Ibid.*

³⁴²FDAR, *supra* note at 71 at C.08.002(2) (e)(f)(g)(h)

In addition to these goals, we might include ensuring that Canadians have access to the drugs they need and that the drugs being brought to market meet the most urgent needs.

Increasingly, policy considerations have begun to add on to the traditional drivers guiding the approval process for new drugs. The process is becoming dominated by new concerns for ‘access’, ‘innovation’ and ‘regulation proportional to risk’. While not inherently negative goals, unchecked these policy considerations have the potential for undermining the overall SEQ standard and the scientific scrutiny applied to new drug approvals. Even more drastically, they represent a shift away from a fear that we may be approving unsafe drugs, in favour of a fear that we may not be approving enough necessary drugs.

In the following chapter, I hope to describe the skewed policy goals that have come to dominate regulatory concerns relating to new pharmaceutical products. Far from a concentration on the safety and ultimate efficacy of the product, the drug regime has come to be dominated by a drive for early access at all costs and a concentration on the economic and commercial merit of new discoveries. By re-aligning policy goals to focus on these new priorities, many regulatory actors may be moving away from their broader mandate of protecting the health and safety of Canadians. Similarly, by making these other elements the dominant policy concerns in drug regulation, we also potentially weaken the quality and quantity of scientific evidence brought to bear on new drug approvals.

In brief, a slanted conception of innovation has meant a focus on sponsoring realizable commercial discoveries and an emphasis on not ‘stifling innovation’, rather than sponsoring truly worthwhile or novel drug discoveries. A focus on increased market access has meant that speed of approval has become the performance indicator rather than thorough scientific review. By speeding up the time involved in review to assure market access and qualifying new discoveries by their economic potential, we may erode the ultimate value and safety of the products which reach the market.

A Relative Standard of Safe: The Faustian Bargain in the Use of Any Drug

Using any drug involves a number of trade offs. As Jerry Avorn suggests, “every drug-use decision is a small Faustian Bargain, with risks and benefits”.³⁴³ In fact, Faustian bargains must be made at each stage in the process that guides a drug to the consumer. As Avorn describes:

A pharmaceutical manufacturer must decide whether to proceed with the costly and cumbersome development of a new molecule that could be a blockbuster product or dead end...An experimental subject must decide whether to volunteer for a trial of a drug that could improve her health or cause unknown hazard. A regulator must decide whether the new product should then be allowed on the market. A physician must decide whether its promised therapeutic value will outweigh its potential for harm. Ultimately, the patient must decide (sometimes several times each day) whether it’s worth taking [a] drug as prescribed.³⁴⁴

Making these trade offs is difficult for all involved and often requires judgments where absolute certainty is impossible. Balancing the unknown is always a “search for a way to structure these trade offs so decisions [can] be made scientifically rather than...by

³⁴³ Avorn, *supra* note 34 at 142

³⁴⁴ *Ibid.*

gut”.³⁴⁵ Yet this balancing of concerns is always an imperfect process which is predicated upon the priorities set and the questions asked.

Every medication has the potential for great good and great harm, and any drug taken at too high a dosage or for too long will invariably prove toxic. Conversely, there are many drugs which, when used correctly, contribute greatly to the lives of Canadians. Antibiotics save thousands of lives each year.³⁴⁶ Developments in treatments for AIDS have enabled us to enhance the lives of those suffering from the disease by decades.³⁴⁷ Diseases such as polio, malaria, and small pox have been suppressed (though not eradicated) in the Northern Hemispheres by public health policies and the judicious administration of medications and vaccines.³⁴⁸ A common perception is that there is a never-ending need for new pharmaceuticals, and as one author notes:

people will always need medicine, and the demographic tilt of the population promises even faster growth as more and more...reach the age of arthritis, osteoporosis, Alzheimer’s and other ailments.³⁴⁹

Drugs have the potential to treat a dizzying number of conditions and potentially address many of the discomforts that come with being ill.

It must be remembered that drugs are foreign substances usually not naturally found in the body in the quantities and concentrations at which they are often

³⁴⁵*Ibid.*

³⁴⁶*Ibid.*

³⁴⁷*Catch 22, supra* note 139.

³⁴⁸W. R. Dowdle, “The Principles of Disease Elimination and Eradication” (1998) 76(S2) *Bulletin of the World Health Organization* 22.

³⁴⁹F. Hawthorne, *The Merck Druggernaut: The Inside Story of a Pharmaceutical Giant* (Hoboken, New Jersey: John Wiley & Sons, 2003) at 178.

³⁴⁹F. Hawthorne, *The Merck Druggernaut: The Inside Story of a Pharmaceutical Giant* (Hoboken, New Jersey: John Wiley & Sons, 2003) at 178.

administered. Drugs can be described by their selective toxicity, hopefully targeting one condition while minimally affecting normal functioning.³⁵⁰ There is great danger in lightly tinkering with the body's delicate homeostasis, even when that homeostasis is out of balance. Predicting harm can be problematic and danger may result from "an exaggeration of the very effect the drug was intended to have, but sometimes the harm seems to come from out of the blue".³⁵¹ There will always be a level of uncertainty associated with the administration of a medication. It is only with caution that a potentially toxic substance should be approved for wide-scale consumption.

In Canada it is assumed that the role of a drug regulator is to help make these Faustian decisions more informed, based on considerations of a product's SEQ. Initial activities of the regulator, rooted in the criminal power to prevent false and misleading advertising³⁵², have expanded (through regulation and policy guidance) to include a broader health promotion and health protection role.³⁵³ As a trade off against immediate access to all products, it is assumed that products available on the market have been conscientiously reviewed for their ultimate safety and utility. It is also assumed that this review in effect mitigates the toxicity of new drugs, by weighing their overall merit for treatment and mitigation of disease. Without this mitigating role, the regulator's oversight of new drugs becomes diminished if not meaningless.

³⁵⁰*Ibid.*

³⁵¹*Avorn, supra* note 34 at 72.

³⁵²Health Canada, "Progressive Licensing Web Site", online: <<http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/index-eng.php>>, [PL Website].

³⁵³*Ibid.*

Balancing the Appropriate Concerns for Regulatory Oversight of New Drugs³⁵⁴

Traditionally the drug approval process has balanced four competing concerns: (1) ensuring that products reaching the market are safe for consumption (safety), (2) proving that these products have the effect claimed (efficacy), (3) sponsoring the development of new drugs (innovation), and (4) allowing for the distribution of these drug discoveries to the widest number of needy patients as soon as is practicable (access).³⁵⁵ Safety and efficacy are generally achieved under the aegis of clinical investigation of new products. Innovation and access should be achieved by sponsoring valuable or needed drug discoveries and ensuring that drugs get to patients without undue delay. Ensuring that these criteria are balanced appropriately can be very precarious. Often efficacy and innovation will pull toward quicker access and fewer market restrictions, while safety and efficacy will pull toward more rigorous oversight and market restriction. While these goals may lead to different priorities, we must be careful that no one aim comes to dominate the others. If regulators afford one of these concerns too much importance, the approval process becomes skewed.

At its most basic, safety means demonstrating that a drug is not toxic. Regulators must ensure that new products entering the market are not inherently noxious substances that will overly harm the majority of those who consume them.³⁵⁶ In practical terms, this

³⁵⁴Please note: In the following section this discussion is limited to those concerns for regulators relating to the pre-approval process in keeping with the general theme of the thesis.

³⁵⁵Please note: I will not be discussing quality in this thesis. This is usually dealt with through a Site Licensing regime that often has varied manufacturer-based criteria that is based on varied conceptions of harm that would apply to all manufactured products. See Health Canada, *Good Manufacturing Guidelines* (Ottawa: Health Canada, 2009), online: < <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/docs/gui-0001-eng.php>>.

³⁵⁶*Avorn, supra* note 34.

means identifying “a level of risk judged so small as to be insignificant or [at] a level of risk deemed acceptable in a specified situation”.³⁵⁷ Early phase clinical trials are the intended mechanisms for identifying the most hazardous potential outcomes for a drug trial. Pre-clinical testing on animals will generally identify products which are outright poisonous. Phase I studies in volunteers will help identify negative unforeseen effects the drugs might have in humans, while Phase II and Phase III studies will demonstrate the effects of the drug on representative populations. These studies generate surrogate end points, or measures of the drug’s effect over a short time, which are used to extrapolate the long-term effects of the drug. Latent toxicity, subtle impairments, or effects which take a longer time to manifest often will not become evident until the drug has been consumed by a larger population.

Efficacy is the demonstration that a drug has the effects that it purports to have. It is important that a drug not only be shown safe to consume, but also that it be shown as effective.³⁵⁸ In order to show that a drug is useful it should demonstrate: “the benefit to be achieved, a medical problem giving rise to the use of the drug, the population affected, and conditions under which the technology is used”.³⁵⁹ As Henry Waxman has noted, “safety and effectiveness are related inextricably, it is meaningless to say that a drug is ‘safe’ except in relation to a specific demonstrated benefit”.³⁶⁰ Safety and toxicity must be measured partially by the justification for introducing a foreign substance to a subject.

³⁵⁷Wiktorowicz, *supra* note 24 at 624.

³⁵⁸See United States of America, Congress, *Assessing the Efficacy and Safety of Medical Technologies* (Washington: U.S. Government Printing Office, 1978).

³⁵⁹H. D. Banta, C. J. Behney & J. S. Willems, *Towards Rational Technology in Health Care* (New York: Springer, 1981).

³⁶⁰H. A Waxman, “A History of Adverse Drug Experiences: Congress has Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs” (2003) 58 *Food & Drug L. J.* 299 at 305 (WL) [Waxman].

The later stage clinical trials, Phase II and Phase III, are designed to determine the relative effectiveness of new drugs, compared to existing or no therapies. In the case of many non-life threatening illnesses, patients receiving a new medication are simply compared to those receiving no treatment at all, in a placebo trial.³⁶¹ Demonstrations of efficacy have also been criticized for focusing on “measures of morbidity and mortality, with less consideration given to life expectancy or psychosocial and functional factors”.³⁶²

As Perrin notes, “sick people need to have access to effective drugs”.³⁶³ Access can best be described as the concern that administrative processes for new drug approvals not be so overly convoluted or lengthy as to prevent drugs from reaching the patients who need them. Access is a double-edged sword because it “embodies the often conflicting interests of personal autonomy and the need to protect or promote the general good”.³⁶⁴ The *Therapeutics Access Strategy* (TAS) is a set of internal changes at the TPD designed to streamline the approval process, by harmonizing with international standards and placing a limit on the time that reviewers may take in evaluating NDS.³⁶⁵ Using the *Cost Recovery Initiative* (CRI),³⁶⁶ industry now pays for half of the cost of new drug

³⁶¹C. Weijer, “Placebo Trials and Tribulations” (2002) 166(5) *CMAJ* 602 (PUBMED).

³⁶²*Wiktrowicz*, *supra* note 24 at 624.

³⁶³*Catch 22* *supra* note 139 at 105

³⁶⁴*Ibid.*

³⁶⁵Health Canada, Therapeutic Product Directorate, *Regulation and Beyond: Progress on Health Canada’s Therapeutics Access Strategy* (Ottawa: Health Canada, 2005) online: <<http://www.hc-sc.gc.ca/hcs-sss/pubs/pharma/2005-therap-strateg/index-eng.php>>

³⁶⁶Health Canada, *Cost Recovery Initiative*, (Ottawa: Health Canada, 2010), online: <<http://www.hc-sc.gc.ca/dhp-mps/finance/costs-couts/index-eng.php>>.

approvals,³⁶⁷ which in theory allows for greater investments into the infrastructure at the TPD and speeds up approvals.

Equally important is that drug regimes sponsor the development of innovative and needed new drugs. This requires the prioritizing of projects, sponsorship of worthwhile research, funding for developing this work, and incentives for researchers to undertake these tasks. Funding innovative drug research has increasingly come to be equated with the commercial viability of the final product.³⁶⁸ CIHR's 'cycle of innovation' seeks to sponsor:

[a] journey from the laboratory to the marketplace, a journey that enhances lives by offering new ways to prevent, diagnose and treat diseases effectively and profitably.³⁶⁹

The incentive for innovation is found in intellectual property law which "guarantees innovator companies ample periods of market exclusivity to recover R&D costs".³⁷⁰ In the end, innovation is seen as a mechanism that uses the market to direct researchers to the most lucrative drugs, rather than a process for sponsoring research into the most valued or needed new drugs.

To all of these elements we might add an additional and often overlooked goal that binds them all together: the greater social good. In order for government to justify its

³⁶⁷See J. Lexchin, "Drug Regulation: Two Paradigms in Conflict" in N. J. Temple & A. Thompson, eds., *Excessive Medical Spending* (Toronto: Radcliff Publishing, 2007) [Excessive].

³⁶⁸J. Atkinson-Grosjean, "Science Policy and University Research: Canada and the USA, 1979-1999" (2002) 2(2) *Int. J. Technology Policy and Management* 102 [Atkinson-Grosjean].

³⁶⁹Government of Canada, Canadian Institute for Health Research, *Commercialization: Where Innovation Takes Flight* (Ottawa: CIHR, 2004), online: <<http://www.cihr-irsc.gc.ca/e/23906.html>> [CIHR Commercialization].

³⁷⁰A. R. McCabe, "A Precarious Balancing Act: The Role of the FDA as Protector of Public Health and Industry Wealth" (2003) 36 *Suffolk U. L. Rev.* 787 at 804 (WL).

intervention, it aims to demonstrate that it is serving those in whose interest it is regulating. Regulators should make decisions on the basis of the safety, efficacy, and the public interest. Presently this is not always the case. Innovation and access have come to be played off against safety and efficacy; the drivers behind the first two are often economic, while the drivers for the second are commonly public safety. In the following section, I will discuss how an innovation policy that focuses purely on sponsoring economic development is eroding drug science and public safety. Next, I will discuss how access has come to equate less the provision of useful new drugs than the allowance of industry and private interests to push for decreased scrutiny of new products. I will reserve a wider discussion of safety and efficacy standards until the next chapter.

Weakening Science by Over-Emphasizing Access

Arguments around access fall along a continuum, with speed of approval traded off against safety and efficacy assurance. At one extreme of this argument is the libertarian, market-access belief that there should be no state-imposed intervention on the availability of new drugs to consumers. Under this conception, free markets will determine the success or failure, and consequently, safety, of new drugs. At the other extreme is a full precautionary prohibition against all new drugs until it has been conclusively demonstrated that they are safe and efficacious. It is a precarious balance that regulators must strike, ensuring that a drug's safety and efficacy are adequately reviewed while not unduly restricting access. Regardless, regulators must always be given adequate time and sufficient evidence to ensure that they are making appropriate decisions.

Increasingly, the focus of access in the drug approval process means less and less the provision of fully assessed products for SEQ; instead, it simply means speedy approval for all drugs.³⁷¹ The result is that traditional prudence in safety standards is being pre-empted to meet targeted approval times.³⁷² The result is a reduction in the amount of time and scrutiny that is applied to research for approval.³⁷³ Plunging headlong into the promise of new treatments, we may fail to ask: What exactly are the risks of these new drugs? In exchange for what added benefit? And how do we know? How do we judge patient need and treatment value or utility? Inherent in these questions is the conflict of “safeguarding the consumer from potential harm against the freedom to choose a course of treatment”.³⁷⁴

(a) Conceptualizing the Problems Underlying Access – A Drug Lag?

As noted in Chapter 1, the approval process for new drugs in Canada is a closed process. New drug approvals are usually made “without public input or access to the information used in decision-making”.³⁷⁵ This has led to criticisms that approvals are “unnecessarily opaque...[and] should set new standards of access to information at all

³⁷¹J. Lexchin, “Drug Regulation: New Directions in Drug Approval” (2004) 171(3) *CMAJ* 229 at 229 (PUBMED) [Lexchin – New Directions] see also J. Lexchin, *Drug Safety and Health Canada: Going, Going...Gone?* (Ottawa: Canadian Centre for Policy Alternatives, 2009) at page 3, online: <<http://www.policyalternatives.ca> > [Going].

³⁷²*Ibid.*

³⁷³*Ibid.*

³⁷⁴*Catch 22 supra* note 139 at 113.

³⁷⁵*Mintzes, supra* note 141 at 3.

stages of the drug review process, enhancing transparency and public confidence”.³⁷⁶

Joel Lexchin has further criticized this poor access to information:

deprived of any independent access to information, health professionals and the public must accept the TPD’s judgments about safety and effectiveness.³⁷⁷

It is difficult to determine which factors regulators are using in determining the needs of patients to access new drugs.

Critics argue that increasingly this limited public openness means new drugs are often approved on the basis of weak scientific evidence and less than thorough investigation. One investigation which assessed the studies used to approve a withdrawn product found that:

[the drug] was not tested in the patient population it was approved to treat, nor was it tested against placebos or any other [comparable] treatment. Thus the studies submitted to Health Canada did not establish [the drug’s] effectiveness for its approved use.³⁷⁸

Instead of focusing on science, a skewed concept of access is shifting the way in which Health Canada reviews new drugs. As Lexchin has noted:

The organization [TD] has accepted the language and, more importantly, the ideology of the private sector and has tailored its activities to ensure that, in the language of its own Business Transformation Strategy ‘it reduce[s] the administration burden on business’. We need new and better drugs to improve the treatment that people receive, but not at the expense of downplaying safety, as is now the case.³⁷⁹

³⁷⁶*Oasis, supra* note 29 at 12.

³⁷⁷*Ibid.*

³⁷⁸*Mintzes, supra* note 141 at 3.

³⁷⁹*Going, supra* note 229 at page 14.

What are the potential implications when a health regulator's policy begins to formulate approaches to drug review and access based on the administrative burdens placed on business?

Increasingly, business conceives of drug access in terms of the lag that occurs as a result of the approval process. They argue that the “drug lag [represents a virtual] ban on new drugs”³⁸⁰ in Canada that prejudices the patient. At its extreme, this conception of access involves the assertion that there should be no government barriers to patients using those medications that they voluntarily decide to consume. Any delay in access is inappropriate. They suggest that “manufacturers [should] have the sole responsibility of convincing physicians and patients that they should use any new drug”.³⁸¹ These proponents of drug lag assert that the true solutions to access involve privatizing review, speeding up approval, relying upon user fees (industry paying for approvals), and increasing reliance on the U.S. approval process.³⁸² Under this conceptualization, safety and efficacy are best overseen by market forces, with informed consumers “disciplining the pharmaceutical market”.³⁸³

³⁸⁰J. R. Graham, *A Lethal Guardian: The Canadian Government's Ban on Prescription Drugs* (Vancouver: Fraser Institute Digital Publications, 2005) at 1, online: <<http://www.fraseramerica.org>> [Fraser Institute] see also B. J. Skinner & M. Rovere, *Access Delayed, Access Denied: Waiting for New Medicines in Canada* (Vancouver: Fraser Institute, 2010).

³⁸¹*Ibid.* at 14.

³⁸²*Ibid.*

³⁸³*Ibid.* at 18.

(b) Letting the Market Decide

From the perspective of many pro-industry lobbyists, “expeditious approval of useful and safe new products...can be as important as preventing the marketing of harmful or ineffective products”.³⁸⁴ John Graham of the Fraser Institute argues that post-market approval is a virtual ban to consumers and that “lengthening the time new medicines are automatically banned only reduces the timelines of new information about their possible adverse effects”.³⁸⁵ According to this argument, the best way to determine the safety and efficacy of new drugs is by testing them on the consuming public. According to Graham, “informed patients could then use the drug while patients who were ignorant or more averse to risk would veer away from it”.³⁸⁶ Reducing approval times ensures that the market can make the appropriate adjustments to the demand for a drug, based on patients’ awareness of the drug’s safety.

Letting the market determine drug safety and efficacy is ethically problematic for at least three reasons. The first is the expectation that a degree of harm should be inflicted on the consuming public to determine a drug’s effects. If there is an opportunity to prevent such harm a priori, there is an obligation on government to minimize it. Secondly, there is an assumption that post-release adverse event reporting is effective in determining the dangers of drugs on the market. Organizations such as the MHPD (the

³⁸⁴See D. G. Parver, “Expediting the Drug Approval Process: An Analysis of the FDA Modernization Act of 1997” (1999) 51 *Admin L. Rev.* 1249 at 1258 (HEINONLINE) [Parver].

³⁸⁵*Fraser Institute, supra* note 380 at 22.

³⁸⁶*Ibid.* at 19.

agency in Canada which monitors ADR) are consistently underfunded³⁸⁷ and adverse events are chronically underreported.³⁸⁸ Finally, there is an assumption that consumers have the capacity to inform themselves of the merits of new drugs. Aside from the host of intentional misinformation regarding the true merits of pharmaceuticals,³⁸⁹ this assertion fails to take note of the disparity in knowledge related to drug use between those who provide medicines (physicians) and those who consume them (patients).

(c) The Government's Strategy: Equating Access with Speedy Approval

The government has adopted a strategy which favours a definition of access conceived in terms of a perceived drug lag. In the 2002 Speech from the Throne, the Government of Canada pledged \$190 million to help:

speed up the regulatory process for drug approvals to ensure that Canadians have faster access to the safe drugs they need, *creating a better climate for research in pharmaceuticals* while preserving the principle that safety is paramount.³⁹⁰

According to Health Canada:

improving access to therapeutics in Canada is a high priority ... that includes not only getting them to market, but also removing barriers that affect public access to health products once they make it to the marketplace.³⁹¹

³⁸⁷Lexchin – *New Directions*, *supra* note 371.

³⁸⁸A. Fletcher, "Spontaneous Adverse Drug Reaction Reporting Versus Event Monitoring: A Comparison" (1991) 84(3) *J. R. Soc. Med.* 341 as reported in J. Lexchin, "Is there Still a Role for Spontaneous Reporting of Adverse Drug Reactions?" (2006) 174(2) *CMAJ* 191 (PUBMED) [Role].

³⁸⁹B. Mintzes, *Direct-to-Consumer Advertising of Prescription Drugs in Canada: What are the Public Health Implications?* (Toronto: Health Council of Canada, 2006), online: <<http://healthcouncilcanada.ca>>, accessed March 11, 2006.

³⁹⁰Canada, Government of Canada, *Speech from the Throne*, February 12, 2002 (Canada, 37th Parl., 1st sess.) [2002 Speech from the Throne].

³⁹¹Health Canada, *Access to Therapeutics Products: The Regulatory Process in Canada* (Ottawa: Health Canada, 2006) online: <http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/access-therapeutic_access-therapeutique-eng.php>.

Yet we are left wondering whether improving access can preserve the principle that safety is paramount. No longer is access being associated with getting safe, effective and promising drugs to market; it is now conceived as getting all new drugs quickly to market,³⁹² regardless of therapeutic merit.

As articulated in the recent policy document *Access to Therapeutic Products: The Regulatory Process in Canada*, it seems that policy-makers accept that rapid access is necessary:

From a public policy perspective, the rationale for rapid access... is simple. Good health benefits everyone. In opinion polls, individuals say it contributes significantly to their quality of life. And governments value it because the nation as a whole benefits socially and economically when everyone enjoys the best possible health.³⁹³

Does speedier access truly equate greater health benefits? Is it possible that seeking to accelerate the rate of approval might erode the scientific scrutiny of new drugs and place the health of Canadians at risk?

The average time for new drug approvals in Canada over the past decade has been just under 22 months or 642 days.³⁹⁴ This is slightly longer than most other G8 countries (except Italy and Japan), including the United States.³⁹⁵ Pro-industry lobbyists argue that this is evidence which “shows that the policy of automatically banning new medicines

³⁹²Going, *supra* note 229.

³⁹³*Ibid.*

³⁹⁴N. S. B. Rawson & K. I. Kaitin, “Canadian and US Drug Approval Times and Safety Considerations” (2003) 37 *The Annals of Pharmacotherapy* 1403 (PUBMED) [Rawson].

³⁹⁵K. E. Thomas, N. McAuslane, C. Parkinson, S. R. Walker & D. K. Luscombe, “A Study of Trends in Pharmaceutical Regulatory Approval Times for Nine Major markets in the 1990s” (1998) 32 *Drug Information Journal* 787 (PUBMED) [Thomas] and N. S. Rawson, “Time Required for Approval of New Drugs in Canada, Australia, Sweden the United Kingdom and the United States in 1996-1998” (2000) 162(4) *CMAJ* 501 (PUBMED) [Rawson II].

harms Canadians far more than it helps them”.³⁹⁶ In their eyes, this delay in approval times prevents patients “from getting medicines that are invented as quickly as they would prefer”.³⁹⁷ Yet, this perspective must be tempered by a healthy scepticism, as Lexchin notes:

From the point of view of return on investment, industry preoccupation with time lines makes perfect sense; whether that preoccupation is warranted from a public health point of view is another question.³⁹⁸

Recognizing that it takes longer to approve a drug does not equate acknowledgment that this delay is a health crisis. It is only in the most severe cases and with the most therapeutically meritorious new discoveries that restricting the public from immediate access causes extensive harm, and there are mechanisms for rapid release (SAP).

(i) The Therapeutic Access Strategy (TAS)

In 2003, the federal government enacted the *Therapeutic Access Strategy* (TAS) to help achieve the goal of greater public access to new drugs. The original aim of the TAS was twofold:

- (1) to ensure that human drugs and other therapeutic products are as safe as possible, accessible, of high quality, therapeutically effective, and used properly; and,
- (2) to make access both timely and cost-effective.³⁹⁹

In articulating a vision for the final outcome of this process, much weight was placed upon re-orienting the whole regulatory process toward efficiency and speed in approvals:

³⁹⁶*Fraser Institute, supra* note 380 at 24.

³⁹⁷*Ibid.* at 12.

³⁹⁸*Lexchin – New Directions supra* note 371.

³⁹⁹Health Canada, *Regulation and Beyond: Progress on Health Canada's Therapeutic Access Strategy* (Ottawa: Health Canada, 2005), online: < <http://www.hc-sc.gc.ca/hcs-sss/pubs/pharma/2005-therap-strateg/index-eng.php> > [Regulation and Beyond].

In a shrinking world, the pace of scientific and technological change, and the speed of innovation mean that the regulatory system must be ready to keep up -- to ensure that Canadians have timely access to new advances in health products, foods, therapies and health technologies, both from Canada and around the world.

This means taking a close look at how we regulate... In the short term, we need to focus on how to move submissions through the review process faster, while still maintaining high standards of safety. The goal is a review system that is *timely, consistent, predictable and of the highest quality*.⁴⁰⁰

These goals were gradually morphed into the concrete policy outcomes of:

(1) ...improving the timelines and transparency of the review process for therapeutic products... (2) enhancing post-market surveillance... (3) improving access to appropriate and cost-effective drug therapies for Canadians.⁴⁰¹

These guidelines seem to indicate a policy shift toward quick approval followed by determination of long-term safety on the consuming public, despite the fact that “availability and wide use are not guarantees of a drug’s safety”.⁴⁰²

Under TAS, a host of new initiatives have been introduced, such as the Drug Products Database (DPD),⁴⁰³ Summary Basis of Decisions (SBD) Database,⁴⁰⁴ and ADR Med Effects Database,⁴⁰⁵ which have the potential for increasing access to the details of new drug discovery. Still, these efforts have been partial and incomplete. Instead the focus of TPD’s short term strategy has been “beating the backlog...reduce[ing] the

⁴⁰⁰*Ibid.*

⁴⁰¹*Ibid.*

⁴⁰²*Lexchin Withdrawals, supra* note 18 at 766.

⁴⁰³Health Canada, *Drug Product Database*, online: <<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php>>.

⁴⁰⁴Health Canada, *Summary Basis of Decisions Website*, online: <<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/index-eng.php>>.

⁴⁰⁵Health Canada, *Med Effect Canada Website*, online: <<http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>>.

backlog of new drug submissions”.⁴⁰⁶ At the same time it is readily admitted that there are “remaining gaps” in achieving the long-term goals of “accelerating access to breakthrough and non-prescription drugs [and] strengthening evaluation of real-world safety and effectiveness”.⁴⁰⁷

Under the TAS, “product submissions are now managed as ‘projects’... that are planned, coordinated, and managed, to meet performance targets”.⁴⁰⁸ The main barometer by which the success of meeting these targets is measured is speed of approval. The *Regulatory Review of Pharmaceutical, Biologics and Medical Devices 2005 Annual Summary of Performance*⁴⁰⁹ conceives of performance strictly as “significant progress made in eliminating the review blockage and towards issuing review decisions within performance targets”.⁴¹⁰ Nowhere is safety mentioned. The TPD now sets a performance target for review, including processing, screening, and review, at 180 days for standard drug reviews.⁴¹¹ As noted in the introduction to the report:

Compared with the year 2003, median authorization times have improved for new pharmaceuticals drugs, dropping by 33% and 29% respectively, for Brand name, Priority and Standard drugs.⁴¹²

This means that the average time to approve brand name standard pharmaceuticals in 2005 was 18.3 months compared with 28.8 months the year before, which represents a

⁴⁰⁶*Regulation and Beyond, supra* note 399.

⁴⁰⁷*Ibid.*

⁴⁰⁸*Ibid.*

⁴⁰⁹Health Canada, *Regulatory Review of Pharmaceutical, Biologics and Medical Devices 2005 Annual Summary of Performance* (Ottawa: Health Canada, 2004), online: <http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/performance_rendement_2004_e.html> [TPD Annual].

⁴¹⁰*Ibid.*

⁴¹¹*Ibid.*

⁴¹²*Rawson II, supra* note 395.

drastic drop of 10 months. One is left wondering what potential accuracy in the review process is lost, given such a sharp drop in the time spent reviewing new drugs.

It is interesting to note that in order for the TPD to achieve its goals of reducing the drug approval backlog, “the number of interim decisions issued increased by 53% since 2003”.⁴¹³ Interim decisions represent a form of approval with the condition that manufacturers provide additional information at a later time. The usual reasons for interim decisions are “deficiencies with respect to the regulatory requirements for market authorization”.⁴¹⁴ Still, regardless of these deficiencies, the TPD is increasingly willing to issue approvals for incomplete applications in order to meet timelines. The ultimate question is whether these deficiencies in product applications might represent gaps in the proof or quality of information submitted for approval.

Part of conceiving of drug approval as a project or deliverable involves placing part of the cost for approval on industry. In 1995, the federal government introduced regulations to charge industry a portion of the cost for new drug approvals.⁴¹⁵ It was believed that these would offset labour, operations, program, and administrative overhead costs.⁴¹⁶ In 2004, the *User Fees Act*⁴¹⁷ (UFA) was passed, which “establish[ed] a link

⁴¹³Lexchin *Withdrawals*, *supra* note 18 at 11.

⁴¹⁴*Ibid.*

⁴¹⁵*Drug Evaluation Fees Regulations*, SOR/ 95-424. See also *Authority to Sell Drugs Fees Regulations*, SOR/ 95-31, *Establishment Licensing Fees Regulations*, SOR/ 98-4. All created under the *Financial Administration Act*, R.S.C. 1985, c. F-11.

⁴¹⁶Progestics International Inc., *Final Report for the Financial Models Project* (Ottawa: Health Canada, 2004) see also J. Lexchin, “Progressive Licensing of Drugs: Music or Noise?” (2008) 3(4) *Health Care Policy* 11 (PUBMED).

⁴¹⁷*User Fee Act*, S.C. 2004 c. 6 [UFA].

between performance and new fees”.⁴¹⁸ Section 1(f) of UFA⁴¹⁹ required approval times to:

establish standards which are comparable to those established by other countries with which a comparison is relevant and against which the performance of the regulating authority can be measured.⁴²⁰

In the case of drug approval times at TPD, this means comparison with international standards, mainly those of the United States. Government bodies charging user fees were also required to report “performance standards in accordance with 1(f) as well as the actual performance levels that have been reached”. In 2005, 66% of regulatory decisions were issued within targets, compared to 39% in 2004, and 13% in 2003.⁴²² Under UFA, the TPD is functionally trying to exponentially increase the pace of new drug approvals.

In 1999-2000, the *Therapeutic Product Program Cost Recovery Initiative* accounted for over 50% to 70% (\$34.7 million) of the TPD’s cost for reviewing new drugs.⁴²³ Under the current *Drug and Medical Devices Cost Recovery Program*, this figure still accounts for a full third of TPD’s operating costs.⁴²⁴ When so much of internal revenue comes from industry, there is a temptation to view them as your clients or stakeholders, and to forget that your true client is the public whose safety has to be ensured.⁴²⁵

⁴¹⁸*Lexchin Withdrawals*, *supra* note 18 at 22.

⁴¹⁹*UFA*, *supra* note 417 at 1(f).

⁴²⁰*Ibid.*

⁴²¹*Ibid.*

⁴²²Health Canada, Therapeutic Products Directorate, *2005 – Annual Drug Performance Report* (Ottawa: Health Canada, 2005), online: < http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/docs/perform-rendement/ar-ra/tpd_dpt_annual_annuel_05-eng.php>, accessed on October 12, 2005.

⁴²³*Lexchin Withdrawals*, *supra* note 18.

⁴²⁴*Going*, *supra* note 229.

⁴²⁵*Ibid.*

If we look to the U.S., whose standards Canada is often trying to replicate,⁴²⁶ we might be wary of the potential dangers of cost recovery. At the FDA, cost recovery has:

impaired reviewers' ability to assess drug safety impartially by fostering a frenetic atmosphere in which the pharmaceutical industry is viewed as the customer and scientific debate is discouraged.⁴²⁷

David J. Graham, the scientist who eventually exposed the dangers of Vioxx, reported that he was repeatedly told to consider "the industry our client"⁴²⁸ and keep his concerns silent. He went on to suggest that a common perspective at the regulator is to consider themselves "not there to serve the public...[instead] an institution that has become a factory for the approval of new drugs [where] safety is not a consideration".⁴²⁹

The drive at the TPD to reduce drug approval times seems quixotic, since there already exist two programs, the Priority Drug Review (PDR) and the Special Access Program (SAP), whose purposes in theory are to ensure that those drugs which are most needed or have significant therapeutic merit can reach patients quickly. Under PDR, there is to be a fast-tracking of reviews for drugs that meet the criteria of being:

Effective treatment, prevention or diagnosis of a disease or condition *for which no drug is presently marketed in Canada*; or,
A significant increase in efficacy and/or significant decrease in risk ...over existing therapies...[that]is not adequately managed by a drug marketed in Canada.⁴³⁰

⁴²⁶Rawson II, *supra* note 395.

⁴²⁷S. Okie, "What Ails the FDA?" (2005) 352(1) *NEJM* 1063 at 1065 (PUBMED).

⁴²⁸PBS NOW, "What's in the Medicine Cabinet?" *The Public Broadcasting Service* (1 July, 2005) online: <<http://www.pbs.org/now/science/fda.html>>.

⁴²⁹*Ibid.*

⁴³⁰*Priority Review, supra* note 118.

Priority review of NDS is to take a maximum of 215 days, including processing, screening, and review. The SAP is designed to ensure that specific patients can gain quick access to drugs unavailable in Canada. As Health Canada indicates:

The Special Access Programme (SAP) allows practitioners to request access to drugs that are unavailable for sale in Canada [for] *patients with serious or life-threatening conditions on a compassionate or emergency basis when conventional therapies have failed, are unsuitable, or are unavailable.*⁴³¹

The SAP is intended as patient specific, case by case approval, and does not equate a wider release of a drug. The PDR and SAP programs administered correctly should in theory deal with specific cases of drug lag.

Unfortunately, neither the PDR nor SAP is being administered to meet their original objectives. A host of new drugs which hardly represent “significant increases” over existing therapies or valuable new managements for diseases are being approved using the PDR. Vioxx was approved using a priority review, even though it was demonstrated to not be a significant improvement over existing arthritis therapies.⁴³² At the same time, the SAP is also being exploited. In 2006 a CMAJ letter indicated that 67% of all SAP requests are for silicon breast implants unavailable in Canada.⁴³³ At the same time, six of the article writers’ applications and appeals for novel HIV drug therapies treating end-stage AIDS patients were denied. This has led the authors of this article to plead:

⁴³¹*Special Access Programme, supra* note 121.

⁴³²*Vioxx Lessons, supra* note 20.

⁴³³T. K. S. Christie & J. S. G. Montaner, “The Perverted Irony of Health Canada’s Special Access Programme” (2006) 174(12) *CMAJ* 1746 at 1746 (PUBMED).

Without disparaging the difficulties experienced by women needing breast implants, we cannot contain our moral outrage at the ineffectiveness of the SAP in dealing with truly life-threatening matter[s].⁴³⁴

(ii) Is there a Drug Lag in Canada?

How great is the Canadian drug lag in the approval of essential new drug discoveries? A 2003 study comparing drug approval times for 268 drugs in both Canada and the U.S. from 1992 to 2002, found an average difference of a little over six months (642 days in Canada versus 454 days in the United States).⁴³⁵ For those drugs which underwent priority review in both countries (28 in total), there was a little less than three months difference (Canada at 256 days and the US at 182 days). For those drugs that the PMPRB would have labelled as breakthroughs or substantial improvements (26 in total), there was a little over five months difference (Canada at 476 days and the U.S. at 318 days). While three months and five months respectively do represent a delay for essential new discoveries, it is dubious that they truly represent a “ban on prescription drugs”.⁴³⁶ In fact, for four of the most prescribed classes of drugs, there was little difference in approval times at all; for cardiovascular drugs, it was 760 days in Canada versus 722 days in the U.S., for psychiatric drugs, 1058 days in Canada versus 1024 days in the U.S., for central nervous system drugs, 567 days in Canada versus 554 days in the U.S., and for anti-cancer drugs, 427 days in Canada versus 385 days in the U.S..

⁴³⁴*Ibid.*

⁴³⁵*Rawson II, supra* note 395. In his analysis, the author noted that any comparison between the U.S. and Canada must be made tentatively since the US Food and Drug Administration (USFDA) employs almost 10 times the staff in drug approvals than the TPD.

⁴³⁶*Fraser Institute, supra* note 380.

(iii) Speed at the Expense of Safety?

At the same time, the U.S. withdrew twice as many of its approved drugs (12 in total) for safety reasons as Canada (6 in total). A difference of only six drugs may seem small, but as Lexchin reminds us:

It is necessary to look beyond the raw numbers to judge the magnitude of the problem of unsafe drugs. Large numbers of people, including vulnerable groups, were exposed to some of these products.⁴³⁷

In Canada, if only 0.1 per cent of the population used a dangerous drug, then roughly over 400,000 patients may have been exposed to potential harm. Lexchin has also noted that as Canada has increased the speed of its approval times over the past forty years in general, it has witnessed an increasing number of drugs withdrawn for safety reasons (41 from 1964 to 2004, with 16 since 1993).⁴³⁸ Other studies have shown that “shortened review times were associated with increases in adverse drug reaction[s], hospitalizations and death[s]”.⁴³⁹ This is occurring at the same time as the number of new or truly novel products entering the market is decreasing.⁴⁴⁰ A recent study by Lexchin, has shown that increased speed of approval at TPD, especially for those approved near the end of the mandatory approval time, has resulted in increased market removal of products post market.⁴⁴¹

⁴³⁷Lexchin *Withdrawal*, *supra* note 18 at 765.

⁴³⁸*Ibid.*

⁴³⁹N. Rudholm, “Approval Times and the Safety of New Pharmaceuticals” (2004) 49 *Eur. J. Health Econ.* 345 at 345 (PUBMED).

⁴⁴⁰See R. A. Bouchard & M. Sawicka, “The Mud and the Blood and the Beer: Canada’s New Progressive Licensing Framework for Drug Approval” (2009) 3(1) *McGill Journal of Law & Health* 50 [Bouchard].

⁴⁴¹*Going*, *supra* note 229.

(d) *True Access for Patients*

The best approach to new prescription drugs is ensuring that scientific and safety standards are not sacrificed in the pursuit of speedier access. According to Health Canada's own website:

Health Canada plays an active role in ensuring that you have access to safe and effective drugs and health products. The Department strives to maintain a balance between the potential health benefits and risks posed by all drugs and health products. Our highest priority in determining the balance is *public safety [emphasis added]*.⁴⁴²

Purposeful access also requires "rigid standards...to protect against serious harms".⁴⁴³ As Perrin notes, this is because "terminally or seriously ill patients are particularly vulnerable to exploitation, especially in the absence of alternative therapies".⁴⁴⁴ Making determinations as to the relative value of new products involves delving deeper into the benefits that drugs are likely to provide. Simply assuming that our regulatory structure should allow for all drugs to be offered more expediently may skew the balance between potential benefits and risks toward questionable benefits in favour of unnecessary risks. Part of the access discussion should require determining the relative need and value of new drugs.

Conceptually, the rationale behind faster approval times is to ensure that necessary drugs reach the patients who need them. It does little good to speed up the time in which new drugs reach the market if they do not ultimately improve the lives of patients. Regulatory mechanisms in place (throughout Health Canada) should ensure that

⁴⁴²Health Canada, Health Products and Food Branch, *Drugs and Health Products: Main Page*, (Ottawa: Health Canada, 2009), online: <<http://www.hc-sc.gc.ca/dhp-mps/index-eng.php>>.

⁴⁴³*Catch 22*, *supra* note 139 at 124.

⁴⁴⁴*Ibid.*

necessary drugs are being produced, that they are not prohibitively expensive or inaccessible, and that patients are given a voice to influence policy-makers' decisions about which drugs are important. Upon closer inspection, it is apparent that many of these goals are not being achieved. New drugs are far more synonymous with 'me-too' products, while drugs that are truly valued or needed are often not produced.⁴⁴⁵

(i) *'Necessary' or Me-Too for New Drugs*

Defining necessary drugs has become a difficult task. Currently, there is a culture in which great efforts are made "to convince health-care professionals that their products should be used for an ever-expanding range of symptoms".⁴⁴⁶ As Goozner notes:

Physicians prescribe medicines at a breakneck pace to an aging, overweight, and out-of-shape American people suffering from (to judge from prescription patterns) in near epidemic proportions high cholesterol, high blood pressure, allergies, depression, arthritis, and diabetes.⁴⁴⁷

Manufacturers strive to "change the way people think about their common ailments to make natural processes need medical treatment".⁴⁴⁸ This is occurring along with additional evidence that "more care doesn't necessarily mean better care".⁴⁴⁹ On the

⁴⁴⁵M. Sawicka & R. A. Bouchard, "Empirical Analysis of Canadian Drug Approval Data 2001-2008: Are Canadian Pharmaceutical Players Doing More With Less" (2009) 3 *McGill Journal of Law and Health* 49, [Sawicka].

⁴⁴⁶*Abramson, supra* note 23 at 98.

⁴⁴⁷M. Goozner, *The \$800 Million Pill: The Truth Behind the Cost of New Drugs* (Los Angeles, University of California Press, 2004).

⁴⁴⁸R. Moynihan & A. Cassels, *Selling Sickness: How the World's Biggest Pharmaceutical Companies are Turning us Into Patients* (Vancouver, Greystone Books, 2005) at 1.

⁴⁴⁹*Abramson, supra* note 23 at 180.

contrary, research suggests that “there is strong evidence that behavior and environment are responsible”⁴⁵⁰ for most preventable illness.

There is little incentive for drug manufactures to produce drugs that treat rare illnesses, affect only limited numbers of people, are politically controversial, or are targeted at poor populations. A recent study looking at tropical infectious diseases, the diseases which kill the largest numbers of people, found that of 1393 drugs developed from 1975 to 1999, only 16 targeted these diseases.⁴⁵¹

As the study’s authors note:

Despite impressive advances in science, technology, and medicine, society has failed to allocate sufficient resources to fight the diseases that particularly affect the poor. . . Market prospects and return on investment dictate the pharmaceutical industry’s investments, leaving many medical needs unmet.⁴⁵²

In those jurisdictions where Orphan Drug regulations have been introduced to sponsor the development of needed pharmaceuticals, drug manufacturers have tended to exploit gaps in this legislation to introduce more quickly products that have potentially large off-label markets.⁴⁵³

In the case of drugs for which there is little political or financial desire to seek approval, little can be done to force a manufacturer to introduce the drug to market. The case of RU-486 is a good example. Listed on the WHO’s *Model List of Essential*

⁴⁵⁰*Ibid.* at 204 and see A. H. Mokhad, J. S. Marks, D. F. Stoup & J. L. Gerberding, “Actual Causes of Death in the United States, 2000” (2004) 291 *JAMA* 1238.

⁴⁵¹P Trouiller, P. Olliaro, E. Toreele, J. Orbinski, R. Laing & N. Ford, “Drug Development for Neglected Diseases: A Deficient Market and a Public-Health Policy Failure” (2002) 359 *The Lancet* 2188 (PUBMED).

⁴⁵²*Ibid.* at 2193.

⁴⁵³*Lessons, supra* note 20.

Medicines, RU-486 (Mifepristone) is an early term abortion pill that can be taken orally. It often represents the least intrusive and safest method by which an abortion can be completed. Unfortunately, it is unavailable in Canada simply because no drug manufacturer is willing to submit a NDS for its use, due to fear of political and economic reprisal. In fact, manufacturers have stated that they “won’t apply to market the drug in Canada until they are invited to do so by Health Canada to ensure they won’t face a hostile government”.⁴⁵⁴ Without a willingness from manufacturers to submit the product for approval, there is no way to employ the regulations to gain wide-scale approval for the drug.⁴⁵⁵

The struggle over how to define a serious illness that warrants special attention or drugs is subject to a host of external pressures. If policy-makers are to appropriately apply priority review or sponsor faster approval times, they must identify those drugs which patients are actually asking for. The main groups through which these voices are heard are Patient Advocacy Groups (PAG) or Health Advocacy Groups (HAG). Unfortunately, it is difficult for policy-makers to determine which of these organizations are expressing legitimate patient concerns and which are simply mirroring the desires of industry. As Sharon Batt suggests, untangling the interests which influence the PAG and HAG can be difficult:

The close correspondence of advocacy groups views with those of their industry sponsors suggests this empowerment is more illusory than real.... Is it coincidental that pharma-funded groups focus their criticisms of government on issues like ‘drug-lag’, access to new drugs ...while groups independent of the industry critique government partnerships with industry

⁴⁵⁴L. Lowe, “The Drug of Choice” *The Coast* (9 March, 2006), online: <<http://www.thecoast.ca/halifax/the-drug-of-choice/Content?oid=958771>>.

⁴⁵⁵*Ibid.*

that have weakened the government's monitoring of drug safety and misleading claims?⁴⁵⁶

Drugs like RU-486 are unlikely to receive funded patient advocacy, compared to new treatments for arthritis or dementia.⁴⁵⁷ This presents an uneven voice to regulators, who may come to conceive of need purely in terms of those lobbies which are most active and, ultimately, well-funded.

The truth is that understanding access in terms of true need means “having independent information about diseases and their treatments, and tools to critically analyze a problem”.⁴⁵⁸ A focus purely on the speed of approval has the potential to reduce the quality of scrutiny that is brought to bear on new drug approvals and, ultimately, to imperil patient safety. As Sharon Batt notes:

the push to speedy drug approvals detracts attention and resources from the careful drug review and post-market surveillance needed to assure drug safety.⁴⁵⁹

Conceiving of access in terms of speed is particularly problematic when we fail to distinguish between “‘breakthrough’ drugs and those that offer little or no therapeutic advantage over existing drugs”⁴⁶⁰ or when we are continually substituting “newer, more expensive medications for older, less expensive ones”⁴⁶¹ with little increase in therapeutic merit.

⁴⁵⁶S. Batt, “Marching to Different Drummers: Health Advocacy Groups in Canada and Funding from the Pharmaceutical Industry” (January 2005) *Women and Health Protection* at 12, online: <<http://www.whp-apsf.ca/pdf/corpFunding.pdf>>.

⁴⁵⁷*Ibid.* at 2.

⁴⁵⁸*Ibid.*

⁴⁵⁹*Ibid.* at 9.

⁴⁶⁰*Ibid.* at 12.

⁴⁶¹A. Silversides, “Monitoring the Price of New Drugs” (2006) 174(11) *CMAJ* 1548 at 1548 (PUBMED).

The erosion of access into a frenetic race to increase approval times for new pharmaceuticals also means that safety potentially suffers. While it is possible that increased approval times may be accomplished without a decrease in the scrutiny applied to new drug approvals, the U.S. example indicates that this is unlikely. Instead, emphasizing speed of approval and relying upon industry funding places pressures on the TPD to favour new drug approvals. It behoves us to remember that:

All medicines can cause harm as well as benefit. Without systematic scientific evidence of benefit, no harmful effect, however rare, is worth the risk.⁴⁶²

Access that is narrowly defined in terms of speed of approval loses sight of this key principle, and potentially favours weak science over good science.

Weakening Science by Emphasizing Innovation?

Sponsoring new drug development is essential to ensuring that the potential benefits of prescription drugs are achieved. In principle, this means that incentives and sponsorship should serve to encourage the research and development of drugs that are truly novel and useful. The extent to which any regulatory regime sponsors the development of such drugs can often be a measure of its success at addressing pressing health and societal needs. It can also be a measure of the degree to which it sponsors truly useful scientific discoveries and the advancement of medicine. Yet we must be cautious about conceiving of the value of new discoveries too narrowly; in doing so, we lose sight of the true value of new drugs, weaken science, and imperil the safety of the public.

⁴⁶²*Mintzes, supra* note 141 at 13.

(a) Defining Innovation

Much of our modern regulatory framework and the rationale for current drug policy is predicated upon sponsoring ‘innovation.’⁴⁶³ Yet it is not with ease that we define this amorphous term in the policy context. The Oxford English Dictionary defines innovation as:

the action of innovating; the introduction of novelties; the alteration of what is established by the introduction of new elements or forms; and, the action of introducing a new product into the market; a product newly brought to the market.⁴⁶⁴

Increasingly, the conceptualization of innovation that policy- and law-makers have adopted has come to reflect the second definition, which reflects a narrowing of the value of discovery to its economic and financial impact on the Canadian economy.⁴⁶⁵ As Pazderka and Stegemann suggest, this favours a:

‘linear model’ of innovation postulat[ing] a sequence running from basic research (science) to applied research and, eventually, product development and marketing.⁴⁶⁶

Such a conceptualization may erode the public interest, with “the subordination of science to the economy”.⁴⁶⁷

⁴⁶³*CIHR Commercialization*, *supra* note 369.

⁴⁶⁴*Oxford English Dictionary*, online ed., s.v. “innovation”, online: <<http://www.oed.com/>>, accessed April 3, 2005. The OED also provided several other definitions which are less relevant such as, “The formation of a new shoot at the apex of a stem or branch, esp. that which takes place at the apex of the thallus or leaf-bearing stem of mosses, the older parts dying off behind; The alteration of an obligation; the substitution of a new obligation for the old.”

⁴⁶⁵See B. Pazderka & K. Stegemann *Patent Policy and the Diffusion of Pharmaceutical Innovation* (Ottawa: Industry Canada, 2001), online: < [http://www.ic.gc.ca/eic/site/ippd-dppi.nsf/vwapj/05%20EN%20V2%20%20Pazderka-Stegeman.pdf/\\$file/05%20EN%20V2%20%20Pazderka-Stegeman.pdf](http://www.ic.gc.ca/eic/site/ippd-dppi.nsf/vwapj/05%20EN%20V2%20%20Pazderka-Stegeman.pdf/$file/05%20EN%20V2%20%20Pazderka-Stegeman.pdf) > [Pazderka].

⁴⁶⁶*Ibid.* at 5-12.

On February 12, 2002, the federal government introduced *Canada's Innovation Strategy*⁴⁶⁸ with two policy documents: *Achieving Excellence: Investing in People, Knowledge and Opportunity*⁴⁶⁹ and *Knowledge Matters: Skills and Learning for Canadians*.⁴⁷⁰ These were the result of a policy which for decades had been moving toward equating the value of scientific developments with the economic product of research⁴⁷¹ and achieving excellence focused on “strengthen[ing] our science and research capacity...to ensure that knowledge contributes to building an innovative economy”.⁴⁷² Through the lens of this policy, innovation became how:

knowledge is applied to the development of new products and services or to new ways of designing, producing or marketing an existing product or service for public and private markets. The term “innovation” refers to both the creative process of applying knowledge and the outcome of that process... [and] has always been a driving force in economic growth and social development.⁴⁷³

Innovation in health research and development was now designed to “contribute to the economic competitiveness, effectiveness of public services and policy, and quality of life of Canadians”.⁴⁷⁴

⁴⁶⁷ *Atkinson-Grosjean, supra note 368* at 112.

⁴⁶⁸ *Innovation Strategy, supra note 27*.

⁴⁶⁹ Government of Canada, Industry Canada, *Achieving Excellence: Investing in People, Knowledge and Opportunity* (Ottawa: Industry Canada, 2003), online: <<http://www.innovationstrategy.gc.ca/>> [Excellence], accessed November 12, 2005.

⁴⁷⁰ Government of Canada, Industry Canada, *Knowledge Matters: Skills and Learning for Canadians* (Ottawa: Industry Canada, 2003), online: <<http://www.innovationstrategy.gc.ca/>> [Skills], accessed November 12, 2005.

⁴⁷¹ *Atkinson-Grosjean, supra note 368*.

⁴⁷² *Excellence, supra note 469*.

⁴⁷³ *Ibid.*

⁴⁷⁴ *Ibid.*

How is innovation to be measured in the development of new pharmaceutical products? Not, as one might expect, in the novelty and utility of the medicines produced, but rather, in the extent to which they have the capacity to generate economic enterprise (usually new patents or commercially viable products).⁴⁷⁵ The result has been a push for pairing funding with commercialization of research and the belief that extensive patent terms are required to ensure the motivation for new innovation. The commercialization strategy is embodied in an “effort to move research from an academic setting to the marketplace”,⁴⁷⁶ while the patent term (20 years at present) is conceived as the best way to ensure that “innovation and creativity can flourish in a growing Canadian marketplace”.⁴⁷⁷

(b) Patent Protections and the Incentives to Innovate?

Under this conception of innovation, patent protections are predicated upon the *incentive to innovate theory*. According to this theory, by “conferring an artificial and limited monopoly”⁴⁷⁸ for long periods, one is likely to encourage the greatest incentive for new drug development. This theory holds that:

too few inventions will be made in the absence of the patent protections because inventions once made are easily appropriated by

⁴⁷⁵Pazderka, *supra* note 465 also see M. Rafiqzaman & A. Mahmud, *Is Canada Still Missing the Technology Boat? Evidence Based on The Quality and Quantity of Innovation* (Ottawa: Industry Canada, 2001) online: <[http://www.ic.gc.ca/eic/site/ippd-dppi.nsf/vwapj/10-EN%20Rafiqzaman-Mahmud.pdf/\\$file/10-EN%20Rafiqzaman-Mahmud.pdf](http://www.ic.gc.ca/eic/site/ippd-dppi.nsf/vwapj/10-EN%20Rafiqzaman-Mahmud.pdf/$file/10-EN%20Rafiqzaman-Mahmud.pdf)> [Missing the Boat].

⁴⁷⁶CIHR *Commercialization*, *supra* note 369.

⁴⁷⁷Government of Canada, Department of Consumer and Corporate Affairs Canada, *Intellectual Property and Canada's Commercial Interests* (Ottawa: Consumer and Corporate Affairs Canada, 1990) at 1.

⁴⁷⁸K. Iles, “A Cooperative Analysis of the impact of Experimental Use Exemptions in Patent Law on Incentives to Innovate” (2006) 4 *Nw. J. Tech & Intell. Prop.* 61 at 63 (WL).

competitors of the original inventor who have not shared in the cost of invention.⁴⁷⁹

This monopoly is a trade-off that allows “the patent holder to profit from the sale of the drug, so as to serve the public interest of having life-improving drugs developed”.⁴⁸⁰ Pharmaceuticals are especially subject to this form of exploitation, since the products can easily be chemically duplicated once they are on the market.

The theory guiding the creation of incentive to innovate operates on two core assumptions. The first is that the patenting of drugs is the best way to encourage worthwhile drug discoveries and innovation; the second is that lengthy patent periods are required to allow drug companies to recoup the massive cost they incur in research and development of new drugs. These assumptions in turn beg at least three questions. How innovative is the drug industry as a developer of essential and needed drugs? How innovative is the Canadian pharmaceutical industry as a driver of economic growth? Finally, how extensive are the research expenditures that drug companies must make to develop a new drug?

How effective is the Canadian pharmaceutical industry as a driver of valuable and novel discoveries? The PMPRB places newly patented drugs into three categories for determining pricing. Category 1 drugs are line extensions of existing drugs, usually measured by changes in dosage. Category 2 drugs are

⁴⁷⁹D. Vader, eds., *Intellectual Property Rights: Critical Concepts in Law*, 3rd ed., (Toronto: Routledge: 2006) at page 87.

⁴⁸⁰*Ibid.*

substantial improvements or ‘breakthrough’ drugs classified as “the first to effectively treat a particular illness or which provides a substantial improvement over existing drug products”.⁴⁸¹ Category 3 drugs are modified drugs or new dosage forms of existing drugs that “provide moderate, little or no improvements over existing medicines”.⁴⁸² In the period from 2000 to 2005, information was available for 342 new patented drugs reviewed by the PMPRB, out of which 179 (52%) were line extensions, 153 (45%) were category 3 modified drugs, and only 10 (3%) were category 2 breakthrough drugs.⁴⁸³ In fact, from the years 2002 to 2004, the PMPRB reported only one drug that they classified as a category 2 substantial innovation.

Approximately 79% of the drugs prescribed in Canada in 2005 were introduced in the last decade. Only 35 of these drugs would be classified as significant innovations by the PMPRB.⁴⁸⁴ Over the same period (1996-2005), drug profits have risen from \$6.6 billion to well over \$11.6 billion.⁴⁸⁵ The vast majority of these drugs have been very expensive while providing questionable increases in therapeutic benefit.⁴⁸⁶ We are seeing the “prescribing of newer, more

⁴⁸¹Government of Canada, Patented Medicines Prices Review Board (PMPRB), *PMPRB Annual Report 2005* (Ottawa: PMPRB, 2005), online: <<http://www.pmprbcepmc.gc.ca>> [PMPRB 2005].

⁴⁸²*Ibid.*

⁴⁸³Please note: The idea for this analysis was generated from a similar analysis conducted for the years 1996-2000 in *Lexchin Where, supra* note 70.

⁴⁸⁴See *PMPRB 2005, supra* note 481 at 21.

⁴⁸⁵*Ibid.*

⁴⁸⁶See S. G. Morgan et al., “‘Breakthrough’ Drugs and Growth in Expenditures for Prescription Drugs in Canada” (2005) 331 *BMJ* 851(PUBMED) [Morgan]. Comparing the above figures with those reported in *IP Lexchin, supra* note 483, between 1996 and 2005 there were a total of 797 newly patented drugs introduced in Canada, of which only 35 were Category 2, 379 were Category 3 and 383 were line extensions.

expensive drugs, in place of older, less expensive, but not necessarily less effective ones”.⁴⁸⁷

The majority of these newer drugs are not novel discoveries, but rather replications or modifications of already existing drugs. These ‘me-too’ drugs often afford drug manufacturers the opportunity to gain a market share or profit from a product that has already proven successful.⁴⁸⁸ Conversely, there is little incentive to develop drugs which treat rare diseases affecting poor or under-represented groups, which are not frequently found in rich, Westernized countries or which are unlikely to turn a profit.⁴⁸⁹ Such ‘orphan drugs’ may be more ethical and needed based on the harm they can prevent, but they cannot be justified on their potential as economic innovations.⁴⁹⁰

How much economic innovation does Canadian drug development sponsor? Drug-makers employ approximately 28,000 individuals in Canada, but the majority of these positions are in the manufacturing sector (19,000) and administration (6000).⁴⁹¹ Canada spends the least of all G8 countries on the

⁴⁸⁷*IP Lexchin, supra* note 483.

⁴⁸⁸For an extensive discussion of me-too drugs see *Angell, supra* note 105 at Chapters 4-6.

⁴⁸⁹In the U.S. and Canada, there are attempts to address this problem by providing additional patent rights to new drug manufacturers, specifically to ensure clinical trials for pediatric products. This legislation has not been completely successful at achieving its intended effects (see *Patent Linkage, supra* note 136). Instead, drug manufacturers seek early approval for products labeled for needy populations for a narrow intended purpose, and then supply the drug to a wide off-label market. See *Catch 22, supra* note 139.

⁴⁹⁰*Catch 22 ibid.*

⁴⁹¹See *Skills, supra* note 470.

research and development of new drugs.⁴⁹² The majority of the \$1.12 billion dollars spent on research in Canada in 2005 went toward applied research (mainly clinical trials for approval), with only 19.7% or \$221.7 million going toward basic (chemical or biological) research. This figure has not risen significantly in the past decade. The percentage of total profits returned to R&D in Canada (8.3%) is the lowest of all G8 countries.⁴⁹³ These amounts do appear to be a significant investment, but represent only a fraction of the funds generated in profits (\$11.6 billion) as a result of patent rights. In 2005, Canada's foreign drug sales accounted for only 3.2% of the international drug market.⁴⁹⁴ Conversely, we are one of the greatest importers of drugs for our domestic market; in 2000, this imbalance accounted for 75.5% of drug purchases in Canada. Rather than acting as a driver of economic growth, drug expenditures suggest a drawing of capital out of Canada's economy.

In fact there is little patent innovation that remains in Canada. The moderate size of Canada's role as an innovator means that most new and viable discoveries are likely to be shipped off-shore. The majority of new patents drugs, even those developed in Canada, are filed first in larger markets such as the United States or European Economic Union.⁴⁹⁵ As one author notes, "Canadian inventors remain motivated to invent by obtaining patents in large foreign

⁴⁹²Government of Canada, Patented Medicines Price Review Board (PMPRB), *A Comparison of Pharmaceutical Research and Development Spending in Canada and Selected Countries*, (Ottawa: PMPRB) at page 19, online: <<http://www.pmprb-cepmb.gc.ca>>.

⁴⁹³*Skills*, *supra* note 470.

⁴⁹⁴*Ibid.* at 33.

⁴⁹⁵*Missing the Boat*, *supra* note 475 at 10-18 & 10-19.

jurisdictions”.⁴⁹⁶ Most major drug manufacturers are in dire need of new discoveries. The R&D to sales ratio of pharmaceutical patentees peaked in the mid 1990s.⁴⁹⁷ Pharmaceutical companies are relying more frequently upon profits and revenues from discoveries made almost twenty years ago, and whose patents are on the verge of expiring.⁴⁹⁸ As one author has suggested:

It would be difficult to rationalize strong patent protection in Canada on the grounds of the motivation of innovation function because the Canadian market is too small to affect more than marginally the R&D policies of pharmaceutical producers who invent new drugs with a view to marketing them all over the world.⁴⁹⁹

Any truly profitable innovations made in Canada are likely to be taken abroad to countries with larger markets and larger research infrastructures.

What of the exorbitant R&D costs that are used by industry to justify extended patent provisions? Industry estimates place the cost to bring a new chemical entity (NCE) to market at \$802 million USD.⁵⁰⁰ Rx & D Canada projects this figure to even more at \$1.3 billion.⁵⁰¹ Commonly quoted by both industry and policy-makers, these figures are highly inflated by the inclusion of costs for development that would normally be considered marketing and advertising,⁵⁰² including losses due to capitalization (i.e., speculative revenue that could have been made investing in equity markets instead of

⁴⁹⁶*Pazderka, supra note 465* at 5-24.

⁴⁹⁷*PMPRB 2005, supra note 481* at 40.

⁴⁹⁸*Patent Linkage, supra note 136*.

⁴⁹⁹*Missing the Boat, supra note 475*.

⁵⁰⁰J. A. DiMasi, R. W. Hansen & H. G. Grabowski, “The Price of Innovation: New Estimates of Drug Developments” (2003) 835 *J. Health Econ.* 1 (LEXIS).

⁵⁰¹Rx & D - Canada’s Research-Based Pharmaceutical Companies, *From Molecule to Medicine* (Ottawa: Rx & D), online: <<https://www.canadapharma.org/en/research/industryfacts/phrmavideo.aspx>>, accessed May 27, 2008.

⁵⁰²*Relman, supra note 148*.

R&D),⁵⁰³ and failing to account for tax deductions. Furthermore, the majority of new drug patents are not novel, but rather reformulations of older existing drugs for which scientific research costs are far lower. It is estimated that the actual out-of-pocket cash investment in researching the most expensive new drugs is closer to \$110 million USD.⁵⁰⁴

In recovering these costs, Canada is only a minor contributor to total international drug sales (approximately 2% of total sales),⁵⁰⁵ suggesting that our share of costs that must be recouped amounts to approximately \$20 million at most, or possibly as little as \$2.2 million per new drug. As one author notes:

when developing global R&D plans, it is unlikely that either investors or managers in global, research-based drug-makers take Canadian policy into account.⁵⁰⁶

In 2010, Canadians spent \$24.5 billion on drugs,⁵⁰⁷ far more than the losses that industry could conceivably have sunk into developing new drugs for the Canadian marketplace.

(c) Commercialization, Innovation and the Degradation of Academic Science

(i) Commercialization of Research

A second consequence of conceiving of innovation purely in economic terms has been a drive toward increased commercialization of drug research. Downie has defined

⁵⁰³Editorial, "Costing Drug Development" (2003) 2 *Nature Reviews: Drug Discovery* 247.

⁵⁰⁴Public Citizens Congress Watch, *Rx&D Myths: The Case Against the Drug Industries 'Scare Card'* (Washington: PCCW, 2001) [Scare Card] as cited in *IP Lexchin*, *supra* note 483 at 254.

⁵⁰⁵Figures adjusted from *IP Lexchin*, *supra* note 483.

⁵⁰⁶*Fraser Institute*, *supra* note 380.

⁵⁰⁷Canadian Institute for Health Information (CIHI), *Drug Expenditures in Canada 1985 to 2009* (Ottawa: CIHI, 2009, online: <http://secure.cihi.ca/cihiweb/products/dex_1985_to_2009_e.pdf> [CIHI 2009].

commercialization as “the converting of research results into products, services, and processes that can be the object of commercial transactions”.⁵⁰⁸ This has been marked by both a push for the development of commercially viable products and an emphasis on public-private partnerships in drug research. The beginning of global commercialization of research occurred in 1980, when the U.S. passed the *Bayh-Dole Act*,⁵⁰⁹ which allowed discoveries made in public institutions and universities to be patented by private industry. Canada has taken much more of a hands-off approach to legislating commercialization, advancing a policy that emphasizes that “partnerships [are] key to expanding innovation opportunities and mitigating risk”.⁵¹⁰

Much of the innovation that occurs in the development of drugs begins with public researchers.⁵¹¹ As one author has noted, “innovation in the drug industry – more so than in most other industries – depends heavily on the diffusion of knowledge from universities and government laboratories”.⁵¹² In the U.S., the largest drug development market in the world, only 15 per cent of new discoveries come from industry, 55 per cent come from National Institute of Health (NIH)-funded institutions, and 30 per cent from academic institutions.⁵¹³ Similarly, in a study which assessed the number of articles cited in new patent applications, it was found that:

⁵⁰⁸J. Downie & M. Herder “Reflections on the Commercialization of Research Conducted in Public Institution in Canada” (2007) 1(1) *The McGill Health Law Publication* 23.

⁵⁰⁹*Bayh-Dole Act or University and Small Business Patent Procedures Act*, 35 U.S.C. § 200-212 (1980).

⁵¹⁰*Excellence*, *supra* note 469 at 9.

⁵¹¹*Angell*, *supra* note 105.

⁵¹²*Pazderka*, *supra* note 465.

⁵¹³*Scare Card*, *supra* note 504.

only 15 percent came from industry, while 54 percent came from academic centers, 13 percent from government and the rest from other public and non-profit institutions.⁵¹⁴

In many cases it may be difficult to separate institutional funding from industry, but regardless the majority of the initial cost are born by public institutions, until a discovery demonstrates market potential.

In Canada, 50 per cent of drug R&D sponsorship, or approximately \$1 billion per year, is spent on research. The majority of this funding goes to applied research (clinical trials) sponsored in public institutions (hospitals or academia).⁵¹⁵ This is a broad trend; in a survey of 122 top U.S. medical schools, the NEJM reported that on average, there were 103 public-private drug review partnerships.⁵¹⁶

Over the past three decades, there has been a slow repositioning of universities and their research as a “component of the national system of innovation”⁵¹⁷ along with the entrenchment of academic science as a commodity that should “contribute to national prosperity”.⁵¹⁸ Commercialization has two potentially limiting effects on science: (i) it binds research closely to industry funding, and in turn, industry objectives and motivations may come to dominate the research agenda; (ii) it operates upon the assumption that the most fruitful scientific research has an apparent and readily realizable market potential. In considering these two outcomes, we must ask what potential

⁵¹⁴D. E. Zinner, “Medical R & D at the Turn of the Millennium” (2001) 20(5) *Health Affairs* 202 as cited in *Angell, supra* note 105 at 64.

⁵¹⁵*Missing the Boat, supra* note 475.

⁵¹⁶K. A. Schulman et als., “A National Survey of Provisions in Clinical-Trial Agreements Between Medical Schools and Industry Sponsors” (2002) 37 *NEJM* 1335 (PUBMED).

⁵¹⁷*Atkinson-Grosjean, supra* note 368 at 103.

⁵¹⁸*Ibid.*

outcomes in relation to safety and access might result from passing drug research into the hands of industry. Even more compelling is the danger that as researchers have to commercialize their research, they will focus on marketable products (such as new drugs) and little research will be done into areas of medicine that have no intrinsic market value (such as health promotion).

(ii) Denigrating the Quality of Drug Research

As increased amounts of research funding comes from industry, private interests may come to believe that their financial stake “buys them the right to set the research agenda”.⁵¹⁹ Critics assert that these partnerships have the potential to denigrate the quality of academic research, discourse, freedom, and science used in drug trials. As Sheldon Krimsky notes, one of the perils of these partnerships is that:

secrecy has replaced openness; privatization of knowledge has replaced communitarian values, commodification of discovery has replaced the idea that university-generated knowledge is a free good, a part of the social commons...[and] an unprecedented rise in conflicts of interest... As universities turn their scientific laboratories into commercial enterprise zones and as they select their faculty to realize these goals, fewer opportunities will exist in academia for public-interest science.⁵²⁰

This degradation in the ethos underlying scientific pursuit not only erodes the quality of science which is pursued, but also limits the questions that researchers are able to ask. It also leaves open the potential for skewing conclusions researchers may draw from research related to safety and efficacy.

⁵¹⁹ *Abramson, supra* note 23 at p. 96.

⁵²⁰ S. Krimsky, *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* (New York: Rowman & Littlefield Publishers: 2003) at 7.

Most clinical trials are performed to “facilitate regulatory approval of a device or drug rather than to test a specific novel scientific hypothesis”.⁵²¹ As the recent case of Canadian researcher Nancy Olivieri shows, with increased financial and contractual ties researchers may lose the freedom to express concerns or meet ethical obligations when these interests conflict with those of sponsors.⁵²² Several widely published reports have demonstrated that studies sponsored by industry are far more likely to have favourable outcomes (almost 4 to 1).⁵²³ Likewise, sponsored research which is unfavourable is far more likely to remain unpublished or to not appear in peer-reviewed journals.⁵²⁴ These biases led the editors of several major medical journals to issue the following statement in 2002:

Scientists have ethical obligations to submit creditable research results for publication. As the person directly responsible for their work, researchers therefore should not enter into agreements that interfere with their access to the data or their ability to analyze the data independently, to prepare manuscripts, and to publish them. Authors should describe the role of the study sponsor(s), if any, in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the report to publication.⁵²⁵

Yet as researchers increasingly become dependent upon industry funding, there are concerns that “economic considerations have become more important than the real purpose of clinical trial[s]”.⁵²⁶ Clinical trials must be careful to not slip into the world of pseudo-science where they are developed merely to meet the minimum requirements of regulatory approval and serve the profit-maximization goals of the private sector.

⁵²¹F. Davidoff et als., “Sponsorship, Authorship and Accountability” (2001) 165(6) *CMAJ* 786 at 786 (PUBMED).

⁵²²J. Downie, P. Baird & J. Thompson, “Industry and the Academy: Conflicts of Interest in Contemporary Health Research” (2002) 10 *Health Law J.* 103.

⁵²³ *Bhadari, supra* note 21.

⁵²⁴ *Outcomes, ibid.*

⁵²⁵H. C. Polk, “Scientific Data from Clinical Trials: Investigator’s Responsibilities and Rights” (2002) 26 *World J. Surg.* 637 at 637 (PUBMED).

⁵²⁶ *Garnttini, supra* note 207.

(iii) Commercialization and the Denigration of Drug Research

If we conceive of science in terms of drugs that can be commercialized, an overemphasis on economic models will move us toward the use of mechanisms of discovery that are the most cost-effective and provide the greatest return on investment. This means that more costly and time-consuming discoveries will be ignored, even if they are likely to prove more useful. The blending of commercial and academic research into new drug discoveries has meant that NCEC research often adopts efficiency models from business. According to one author:

This new concept [means] the critical discourse between chemists and biologists and the quality of scientific reasoning are sometimes replaced by the magic of large numbers.⁵²⁷

The development of new drugs has seen a shift in emphasis on innovation from developing products for specific illnesses, to developing drugs that modify specific physiological or molecular mechanisms, or *modes of action* (MoA). It is easy to test a NCE's effect on an MoA, since large numbers of compounds can be reviewed quickly and cheaply in in-vivo cell cultures.⁵²⁸

This has the result of pushing industry-funded drug research toward “focusing on known targets [MoA] and using existing drugs in new indications”⁵²⁹ rather than into novel drug development. As one author notes, this approach to drug discovery further limits:

⁵²⁷J. Drews, “Drug Discovery: A Historical Perspective” (2000) 287 *Science* 1960 at 1962 (PUBMED).

⁵²⁸*Ibid.*

⁵²⁹F. Sams-Dodd, “Drug Discovery: Selecting the Optimal Approach” (2006) 9(11) *Drug Discovery Today* 465 at 465 (PUBMED).

the possibility of letting biology and chemistry deliver serendipitous discoveries ... because [observation] is restricted to known mechanisms and biological processes for which we can provide a theoretical framework for their role in the disease.⁵³⁰

Understanding that a compound has the capacity to manipulate a mechanism does not equate to a fulsome understanding of the global effect that substance has on the body. Drugs that target mechanisms are far more likely to be “symptomatic [treat symptoms] rather than disease modifying treatments”.⁵³¹ Such drugs might be demonstrated as effective, but may not represent optimal or even worthwhile treatments, and certainly lose a degree of tailoring to the specific illnesses from which patients are suffering.

The reliance of drug discovery on the research into MoA has also had the effect of decreasing research that uses other methods of drug discovery. Other approaches such as function-based and physiology-based approaches,⁵³² seek to identify drugs based on their therapeutic effect and merit, and then isolate their mechanisms of action. Both of these approaches are adaptive strategies that “allow researchers to capture rapid changes in health care provision and their implications more quickly”.⁵³³ They are also far more likely to generate novel drugs. Unfortunately, they are far more expensive and resource-intensive, and far less likely to be funded by industry.⁵³⁴

It is dangerous to believe that all worthwhile discoveries will result from the pursuit of commercially viable products. Epistemologically, it has been suggested that

⁵³⁰*Ibid.* at 470.

⁵³¹*Ibid.* at 471.

⁵³²*Ibid.*

⁵³³D. Mechanic, “Lessons from the Unexpected: The Importance of Data Infrastructure, Conceptual Models, and Serendipity in Health Services Research” (2001) 79(3) *The Milbank Quarterly* 459 (JSTOR).

⁵³⁴J. A. Sager & C. Lengauer, “New Paradigms for Cancer Drug Discovery?” (2003) 2(4) *Cancer Biology Therapy* 178 (PUBMED).

there is “no such thing as a logical method of having new ideas, or a logical reconstruction of the process”.⁵³⁵ It is difficult to identify a priori the method most likely to generate new discoveries. Commercial ‘innovation’ into drug research is often retrospective. As George Hitchings, winner of the 1988 Nobel Prize for Physiology and Medicines, notes:

Much of the basic research supported by industry is, in a sense, retrospective. A semi-empirical discovery of a useful drug provides the stimulus for deeper probing into how and why it works, and thus deeper understanding of the underlying disease.⁵³⁶

According to this view, “basic science [is] more often the result than the cause of drug discovery”.⁵³⁷ This explains the permeation of the market with ‘me-too’ drugs, as initial discoveries fuel a host of parallel discoveries that further enhance, refine, or even mimic the initial discovery. Truly innovative discoveries are rare, and seldom the fastest way to return investment on R&D dollars. They are also often simply harder and involve a greater long-term investment in a broad variety of research, with many dead ends.

Discoveries may also be subject to what I call *innovative lag*, a period during which the recognition of a discovery’s value therapeutically or commercially does not occur contemporaneously with its initial development. Often the recognition of a discovery’s value takes time, and comes about after the occurrence of an event such as a new disease, or the development of new technology. This lag may cause a gap before the new idea is disseminated or put to use by the academic community; AZT is an example.

⁵³⁵Popper, *supra* note 2 at 8.

⁵³⁶G. H. Hitchings, “Relevance of Basic Research to Pharmaceutical Invention” (1979) 1 *Trends in Pharmacological Science* 167 at 167 (PUBMED).

⁵³⁷V. Quirke, “Drugs by Serendipity or by Design? Applying Science to the Pharmaceutical Industry in 1950s Britain and France” EBHA Conference 2001: Business and Knowledge.

The pursuit of an immediate financial gain or deliverable from research ignores the possibility that this lag may occur. Instead, research concentrates efforts into discoveries whose applicability is immediately apparent. Not acknowledging innovative lag, and focusing on the immediacy of gain, is far more likely to produce the refinement of a technology rather than the discovery of a new technology. In this way, innovation ceases to be innovative.

The reduction of drug development to economic innovation has the potential to compromise the safety and value of drug research. As Atkinson-Grosjean has noted, “the ‘social contract’ between science and society is being rewritten around economic goals”.⁵³⁸ The search for new drugs now equates the economic impact of new discoveries rather than their inherent therapeutic or scientific worth. This may erode both the quality of scientific research and the quality of products that reach the market. It has also institutionalized a paradigm of research that favours defined research which produces immediately assessable results over exploratory drug research. As a result of this model, safety and efficacy research that operates without the purpose of confirming drug approvals becomes increasingly rare.⁵³⁹ Little funding exists for research into drug safety and efficacy that does not serve this goal.⁵⁴⁰

Falling prey to such a limited notion of innovation brings the peril that important research questions will not be asked or funded. As Kuhn notes in *The Structure of Scientific Revolutions*, dwelling too closely on one conception of

⁵³⁸ Atkinson-Grosjean, *supra* note 368 at 103.

⁵³⁹ Angell, *supra* note 105.

⁵⁴⁰ *Ibid.*

scientific advancement means that only limited questions will be asked. Research that fits the dominant paradigm, in this case economic innovation, represents “the only problems that the community will admit as scientific or encourage its members to undertake”.⁵⁴¹

The result is that “other problems, including many that had previously been standard, are rejected as metaphysical...as just too problematic to be worth the time”.⁵⁴² Safety and efficacy do not easily translate into economic gain.

Under present circumstances, clinging to a narrow conception of innovation:

insulates the community from those socially important problems that are not reducible to the [dominant] norm, because they cannot be stated in terms of the conceptual and instrumental tools the paradigm supplies.⁵⁴³

Where general research into safety and efficacy cannot be translated into economic terms, it may be valued less by those in industry and government who hold the funding purse strings.

⁵⁴¹*Ibid.* at 37.

⁵⁴²*Ibid.*

⁵⁴³*Ibid.*

CHAPTER 5: THE FUTURE DIRECTION OF DRUG REGULATION IN CANADA

Introduction

On April 8, 2008, the Conservative Government of Canada introduced Bill C-51, *An Act to Amend the Food and Drug Act and to make Consequential Amendments to Other Acts*.⁵⁴⁴ The goal of C-51 was to update the 40-year-old *Food and Drug Act*⁵⁴⁵ while at the same time enhancing consumer safety. As the government indicated at the time the Bill was introduced:

Bill C-51 seeks to modernize the dated provisions of the Food and Drugs Act and other Acts concerning the safety quality of food, drugs...especially to strengthen compliance and enforcement measures and empowering the government to order mandatory product recalls.⁵⁴⁶

Generally, C-51 provided for expanded inspection, enforcement powers, and broader regulatory-making powers, actively tried to address previous regulatory gaps, and shifted to approvals based on product risk-benefit profiles.⁵⁴⁷

The preamble to C-51 highlighted that the “objective of protecting, promoting and improving human health”⁵⁴⁸ was still paramount and to be achieved through “a commitment to the health and safety of the public”.⁵⁴⁹ Yet the preamble also hinted at two additional considerations that were underlying the changes proposed by the new Act. The

⁵⁴⁴*An Act to Amend the Food and Drug Act and to Make Consequential Amendments to Other Acts, 2008*, Bill C-51, First Reading, April 8, 2008 (Canada, 39th Parl., 2nd sess.) [C-51].

⁵⁴⁵*FDA*, *supra* note 89.

⁵⁴⁶*C-51*, *supra* note 544.

⁵⁴⁷See, Canada, Parliament of Canada, *Legislative Summary: An Act to Amend the Food and Drug Act and to Make Consequential Amendments to Other Acts* (Ottawa: Parliament of Canada, 2008), online: <<http://www2.parl.gc.ca/Sites/LOP/LegislativeSummaries/Bills>>, [C-51 Summary].

⁵⁴⁸*C-51*, *supra* note 544.

⁵⁴⁹*Ibid.*

first was a shift to a life-cycle model of risk mitigation, recognition that:

Ongoing assessment of information about a therapeutic product over its life-cycle is required both before and after it reaches the market in order to support its safe use.⁵⁵⁰

The other is a shift to approval based on a product's risk-benefit profile where "the assessment of benefit and risks"⁵⁵¹ is "based on scientific and objective evidence".⁵⁵² Yet inherent in this new risk-benefit standard is a belief that lack of scientific certainty should not restrain approval in the case of serious or irreversible conditions:

The [government] recognizes that a lack of full scientific certainty is not to be used as a reason for postponing measures that prevent adverse effects on human health if those effects could be serious or irreversible.⁵⁵³

Underlying these changes is a shift away from Safety Efficacy and Quality (SEQ) standards based strictly on precautionary certainty and a 'point in time' approach to a life-cycle model of drug oversight based on 'risk assessment'.⁵⁵⁴

This new risk-benefit life-cycle model will rely on a host of new regulatory and scientific tools, risk-benefit assessment, pharmacovigilance planning, risk mitigation planning, risk management plans, surrogate end points, and enhanced adverse event reporting. Central to all of these tools is the concept of 'pharmacovigilance'.

Pharmacovigilance has been defined as a set of tools that are used to oversee a product's safety throughout its development, regulatory approval and introduction, and on into use

⁵⁵⁰*Ibid.*

⁵⁵¹*Ibid.*

⁵⁵²*Ibid.*

⁵⁵³*Ibid.*

⁵⁵⁴*PL Website, supra note 352.*

with the consumer.⁵⁵⁵ Competing models in the U.S. and EU have meant that the application of pharmacovigilance can have very different implications for safety and the level of regulatory scrutiny applied to products before they are approved. How these tools will be applied and affect product safety still remains to be determined in Canada.

The other essential new element of the proposed new model is risk-benefit assessment, which would supersede the traditional onus to establish certainty of SEQ. Defining exactly what is meant by a ‘risk-benefit’ analysis is a little more difficult. Health Canada defined a risk-benefit analysis as:

A method of evaluating the usefulness of a drug for a specific indication, taking into account the benefits and risks associated with that drug under normal conditions of use.⁵⁵⁶

Defining the variables to be considered in a risk-benefit analysis (what is a benefit; what is a risk) and how they are to be weighed is no simple process, and both bias and the value assigned to variables must continually be re-evaluated and assessed. There are methods for conducting risk-benefit analysis well, poorly, and some which will always be prone to bias. In the case of new drug approvals, any models adopted must be careful to rely upon clear science and SEQ concerns, rather than allowing bias or external (non-safety-related) factors to dominate the process.

The ultimate impact of these proposed changes on the drug approval and safety

⁵⁵⁵See, World Health Organization, *Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre* (Geneva: WHO, 2000), online: <<http://apps.who.int/medicinedocs/en/d/Jh2934e/3.html#Jh2934e.3>> [WHO PvP], and the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), *Draft Guideline - E2E: Pharmacovigilance Planning* (Geneva, ICH, 2003), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/consultation/e2e_step2_etape2-eng.php#1>, [E2E].

⁵⁵⁶*PL Website at Glossary, supra* note 352.

monitoring process is unclear. What is clear is that these models should be adopted in such a way as to not compromise safety or allow questionable products onto the market.

As the Progressive Licensing Project has acknowledged:

The scientific and regulatory ability to establish whether or not a drug works and to identify risks has become complicated to the point where it has become a field of its own, as have the instruments and methods for monitoring drugs and managing risks once the drug is marketed.⁵⁵⁷

Ingrained in these tools is a shift for regulators from “the traditional gatekeeper role of the past to [one] as information provider and risk manager”.⁵⁵⁸ Both pharmacovigilance and risk-benefit models are new tools for drug regulators. There is much to appreciate in the proposed model; at the same time, poorly designed and applied pharmacovigilance and risk-benefit models could be disastrous. If these changes are going to underlie the new life-cycle approach, it must be ensured that they are developed and explored by regulators in such a way as to enhance the safety of new drugs.

The purpose of this chapter will be to explore the emerging trends in drug regulation in Canada and to comment on the appropriate application of these new tools. Used correctly, these tools hold promise; used poorly, they could severely hamper the role of the federal drug regulator and ultimately, the safety of Canadians. This exploration will begin with a brief look at the policy initiatives which have led to the development of the proposed new drug regime. Secondly, the concrete proposals to change the *Food and Drug Act* proposed by Bill C-51 will be explored. The new life-cycle drug approval model will then be described. Next, risk-benefit assessment and pharmacovigilance as the two key elements of the proposed new regime will be explored. The core principles

⁵⁵⁷ *PL Concept Paper*, *supra* note 58.

⁵⁵⁸ *Ibid.* at page 4.

underlying these models will be described, and their benefits and risks as new regulatory tools will be analyzed. Finally, some general conclusions will be provided.

The Pull Towards a Life-Cycle Model

Bill C-51 was the final outcome of several policy initiatives that had come together to reformulate and modernize the regulation of drugs, most notably the Health Products and Food Branch (Health Canada) *Blueprint for Renewal*,⁵⁵⁹ the Progressive Licensing Project⁵⁶⁰, and the *Food and Consumer Safety Action Plan*.⁵⁶¹ The language of each of these initiatives has moved toward increased post-market surveillance, modernization, a life-cycle approach and empowering the consumer. The general trends encompassed by these initiatives include a slow movement away from precautionary principles of scientific proof toward risk-benefit analysis, and from our present point in time model of drug approval toward a life-cycle model of drug approval.

(a) Health Canada's Blueprint for Renewal

The Health Products and Food Branch (HPFB) began an overall review of its regulatory structure and practices in 2006. The *Blueprint for Renewal*, announced October 2006, was Health Canada's "approach to modernizing the regulatory system for

⁵⁵⁹Health Canada, *Blueprint for Renewal: Transforming Canada's Approach to Regulating Health Products and Food* (Ottawa: Health Canada, 2006), online: < <http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/blueprint-plan/index-eng.php>>, [Blueprint].

⁵⁶⁰See *PL Website*, *supra* note 352.

⁵⁶¹See Health Canada, *Healthy Canadians*, online: <<http://www.healthycanadians.gc.ca>>, and *Report of the Food and Consumer Safety Action Plan Consultation*, (Ottawa: Health Canada, 2007), online: <http://www.healthycanadians.gc.ca/pr-rp/action-plan/2008-safety-securit-tech_e.html> [FCSAP], accessed December 8, 2008. (It should be noted that this report has been removed from the Web).

health products and food[s]”.⁵⁶² The *Blueprint*’s objective is to:

Transform our legislative, regulatory, and policy frameworks [to] make the Branch more efficient, effective, and responsive to help us meet the evolving needs of Canadians in a world of fast-paced change.⁵⁶³

With over 20 separate initiatives within its ambit,⁵⁶⁴ the *Blueprint* represents the single largest shift in policy initiatives for the regulation of health products in the past 30 years.

As part of this initiative, the *Blueprint* initially identified seven objectives directly related to drug regulation. These included:

1. developing a life-cycle regulatory approach to health products that would encompass all stages of product development and use;
2. developing a more transparent and consistent system of categorizing products and assessing their risks;
3. moving away from a reactive waiting for events regulatory system and developing a more proactive approach;
4. better generat[ing], disseminat[ing] and respond[ing] to safety and effectiveness data for health products and food and develop[ing] a more proactive, post-market evaluation strategy;
5. strengthening leadership on a range of health and safety issues affecting specific populations;
6. promoting a more open and transparent regulatory system; and
7. better synchroniz[ing] the regulatory system with the objectives, policies and practices of the health care and innovation systems.⁵⁶⁵

Overall, the initial proposed objectives centered around the life-cycle approach, improving regulatory efficiencies, increasing the effectual use and dissemination of information, and employing measures which categorize and assess their risks.

Consultations on these initial proposals led to a second document, *Blueprint for*

⁵⁶²*Blueprint, ibid.*

⁵⁶³*Ibid.*

⁵⁶⁴These include; The Natural Health Products Regulatory Review, Division 5 Clinical Trial Review., Progressive Licensing, Cost recovery Initiative, The Cosmetic Drug Interface, and others, see *Blueprint, supra* note 559.

⁵⁶⁵*Blueprint, supra* note 559 at page 16.

Renewal II: Modernizing Canada's Regulatory System for Health Products and Food,⁵⁶⁶

with the inclusion of two additional objectives:

- (a) putting in place better legislative, regulatory and policy tools to better support compliance and enforcement; and,
- (b) work[ing] with partners in the health care system to make available more and better information about health products and food to enable Canadians to make informed decisions about their health.⁵⁶⁷

These additional considerations introduced the ideas of informed consumer choice and increased compliance and enforcement powers and penalties.

Underlying these assumptions are several key policy changes in relation to the way that drugs are currently regulated. The *Blueprint* is the first document to introduce the concept that drugs should be assessed throughout their life-cycle, which would allow for the “continuous evaluation of safety and effectiveness and quality of products before and after their introduction to the Canadian market”⁵⁶⁸ and the removal of “traditional regulatory process as a barrier to access”⁵⁶⁹ for urgently needed products. The second is a shift based on risk where “regulatory interventions are proportional to risk and program investments are focused on higher-risk products”.⁵⁷⁰ Third is a move toward a regulatory system that “adapts to new science and technology [in achieving internal and] international benchmarked performance targets for regulated products”.⁵⁷¹ Fourth is the concept that a key part of the drug regulatory process is ensuring that consumers have

⁵⁶⁶Health Canada, *Blueprint for Renewal II: Modernizing Canada's Regulatory System for Health Products and Food*, (Ottawa: Health Canada, 2007), online: <http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/blueprint-plan/blueprint-plan_11-eng.php> [Blueprint II].

⁵⁶⁷*Ibid.* at page 8.

⁵⁶⁸*Blueprint*, *supra* note 559 at page 7.

⁵⁶⁹*Ibid.*

⁵⁷⁰*Ibid.*

⁵⁷¹*Ibid.*

increased capacity to make “informed consumer decisions about their health”.⁵⁷²

Encouragingly, the Blueprint also outlines provisions for increasing openness and transparency in regulatory decision-making and the dissemination of health information learned to practitioners and regulators during a drug’s life-cycle.

In articulating the objective of the *Blueprint*, several key critical success factors were identified by Health Canada. These include:

- (a) A 21st century toolkit of legislation, regulatory frameworks and instruments
- (b) Internationally benchmarked regulatory practices, processes and risk management
- (c) A sustainable, high performance, science-based organization
- (d) Strategic international regulatory cooperation
- (e) Enhanced partnerships and stakeholder involvement.⁵⁷³

These objectives are centered on regulatory modernization through selectively applied regulatory instruments and improved regulatory efficiencies by “meet[ing] performance targets for all regulatory products by increasing regulatory science and foresight capacity”.⁵⁷⁴ These measures involve increasing the degrees of regulatory cooperation, adopting tools and standards, and increasing coordination between domestic and international partners. In effect, this means modernizing Canada’s regulatory system to be reflective of international trends and norms for drug approvals and the adoption of risk management and assessment methodologies.

⁵⁷²*Ibid.*

⁵⁷³*Ibid.* at page 26.

⁵⁷⁴*Blueprint II, supra* note 566 at page 8.

(b) The Canadian Food and Consumer Safety Action Plan (CSAP)

A second document integral to understanding the future development of the Canadian drug regulatory regime is the *Canadian Food and Consumer Safety Action Plan*⁵⁷⁵ (CSAP). The CSAP was released in 2008 as part of the Conservative Government's pledge to "introduce measures on food and product safety to ensure that families have confidence in the quality and safety of what they buy",⁵⁷⁶ as articulated in the 2007 Speech from the Throne. Overall, the CSAP has three principles:

- (a) industry has a responsibility for the safety of products it brings onto the market;
- (b) consumers and health professionals need access to accurate information to make informed decisions;
- (c) government must have the clear authority it requires to address health and safety risks.⁵⁷⁷

Again, the CSAP will have "a focus on active prevention, targeted oversight and rapid response".⁵⁷⁸

Underlying this language is the approach that "oversight should be placed where risks are greatest over the life-cycle of a product".⁵⁷⁹ Targeted oversight shifts the focus from "pre-market review to one that continuously assesses a product's risks and benefits"⁵⁸⁰ with the distribution of responsibility between government, industry, health professionals, and the consumer, and with government intervention at those points perceived to pose the

⁵⁷⁵*FCSAP, supra* note 561.

⁵⁷⁶Government of Canada, *Speech from the Throne*, October 16, 2008 (Canada, 39th Parl., 1st sess.) [2008 Speech from the Throne].

⁵⁷⁷*FCSAP, supra* note 561.

⁵⁷⁸*Ibid.*

⁵⁷⁹*Ibid.*

⁵⁸⁰*Ibid.*

greatest risks.

The CSAP content related to drugs has much in common with the *Blueprint*, articulating six specific goals related to the health products or drugs. These include:

- (a) Taking a life-cycle approach through Progressive Licensing
- (b) Increasing the reporting requirements on industry and health professionals related to ADRs
- (c) Improving compliance and enforcement powers in legislation
- (d) Making fines and penalties more effective
- (e) Improving import safety and improving information for consumers and decision-makers.⁵⁸¹

Again, the life-cycle model takes precedence, along with increased enforcement powers for regulators. The focus is on enabling consumer choice and spreading oversight throughout the life-cycle. As the report indicates:

The Action Plan aims to prevent safety problems by giving consumers and health professionals more and better information to make informed decisions about the safety and safe use of products and by enabling safety planning at an early stage. Enhanced targeted oversight will be achieved by new measures to support the ongoing assessment of the risks and benefits of a product over its life-cycle through a progressive licensing system and by providing modern inspection authorities.⁵⁸²

Increased enforcement powers will be tied to applying regulatory interventions proportional to risks:

Risk-based decision-making requires that the regulator have a wide array of compliance and enforcement tools at its disposal, so that it may choose the most appropriate response to mitigate risk in any situation.⁵⁸³

Again, the intention is that there will be an increase in regulation where risks have been defined as highest and potentially a pull back in regulation where risks are low.

⁵⁸¹ *Ibid.*

⁵⁸² *Ibid.*

⁵⁸³ *Ibid.*

(c) Progressive Licensing

Flowing from the *Blueprint for Renewal*, the Progressive Licensing Project (now the Office of Legislative and Regulatory Modernization [OLRM]), was established in 2006 to “develop a drug regulatory system for the future (to) ensure that Health Canada is capable of maintaining and enhancing its reputation as a science-based and reliable regulator”.⁵⁸⁴ The need for this new regulatory system was identified because of the “rapid worldwide change in response to the advances in pharmaceutical sciences, drug development, and changes in public expectations”.⁵⁸⁵ As PL has acknowledged:

The repercussions from large-scale drug withdrawals indicate potential gaps between what the public expects of the regulatory system and what the system can actually deliver.⁵⁸⁶

To achieve these objectives, PL will move review from “a focus on the pre-market review...to a life-cycle approach that takes into account the entire suite of knowledge gained throughout a drug’s life”.⁵⁸⁷ The proposed model will rely on increased risk management and pharmacovigilance, as well as “anticipate and accommodate changing technologies and methodologies”⁵⁸⁸ for clinical proof of safety and efficacy.

Instead of a point in time approach, the knowledge and clinical information gained about a product’s safety will continue throughout the regulatory process. New drug applicants will be expected to provide commitments for the monitoring and evaluation of their products that will enable continuous evaluation of safety and efficacy

⁵⁸⁴ *PL Website, supra* note 352.

⁵⁸⁵ *Ibid.*

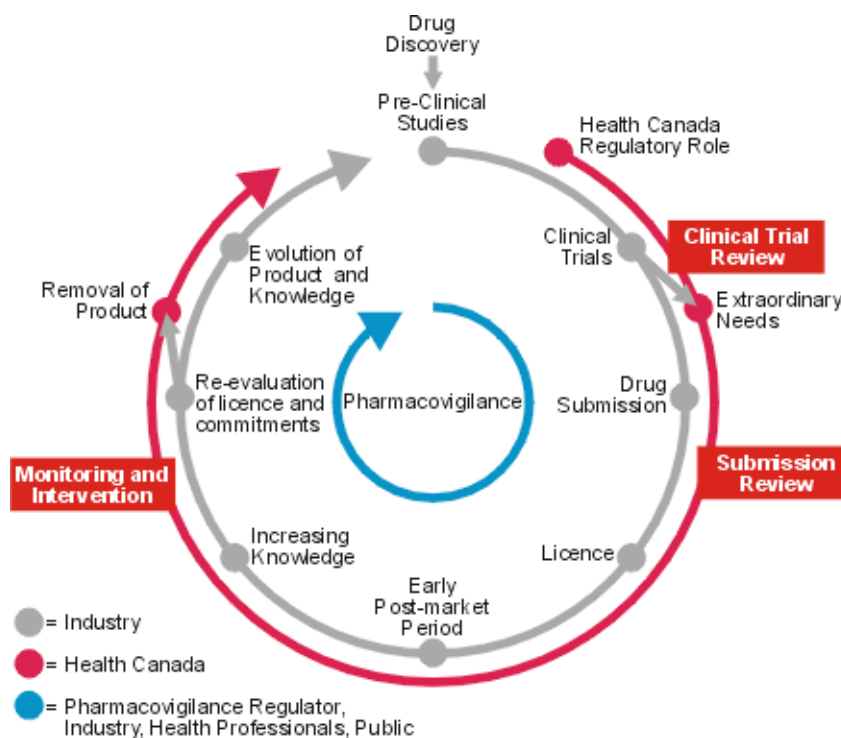
⁵⁸⁶ *Ibid.*

⁵⁸⁷ *Ibid.*

⁵⁸⁸ *Ibid.*

throughout the drug’s life-cycle. Approval will be dependant upon the overall risk and benefit associated with a product, including the product’s capacity to provide promising therapies and the mitigation measures in place to address risks or unknowns associated with a product. As more information is gained about the product, its risk-benefit profile will be modified and the product’s license and commitments placed on the manufacturer will be re-evaluated. If, over time and with increased knowledge the risk-benefit profile comes to weigh on the negative, the product will be removed from the market.

Figure 1: The Progressive Licensing Model⁵⁸⁹



Underlying PL is the concept that improved information related to risk will enhance access by increasing informed consumer choice where “patients are requesting

⁵⁸⁹ *Ibid.*

greater autonomy in making drug choices, including choosing their acceptable levels of risk”.⁵⁹⁰ Approval now shifts from a point in time approach to one in which real-world experience is essential:

rather than placing the focus primarily upon pre-market assessment, this represents a fundamental shift from the idea that the pre-market testing of a drug assures safety and efficacy. The new proposed model is that a drug should be evaluated throughout its life-cycle for its benefit-risk profile.⁵⁹¹

Essential to the model is establishment of “expectations for identifying and managing drug benefits and risks...ahead of marketing for each drug”.⁵⁹² The life-cycle then better mirrors the actual considerations for licensing a drug, in order:

that a favorable benefit-risk profile has been established on the basis of sufficient evidence, a high quality has been demonstrated, and a sufficient life-cycle management plan [pharmacovigilance] has been filed by the manufacturer to allow for introduction of the drug to the market.⁵⁹³

This represents a significant movement away from the point in time SEQ onus on industry to prove drug safety, to ongoing risk-benefit analysis as the basis for a drug’s market authorization. This model has great potential to provide real-world safety and efficacy evidence, but its success or failure will depend upon how risks and benefits are weighed, and the tools in place to ensure the ongoing collection of safety data.

Bill C-51 and the Progressive Licensing Model

The first hint at how the life-cycle model will manifest itself, at least in law, was

⁵⁹⁰*Ibid.*

⁵⁹¹*PL Concept Paper, supra* note 58 at 4.

⁵⁹²*Ibid.* at 5.

⁵⁹³*Ibid.*

provided when the Conservative Government tabled Bill C-51.⁵⁹⁴ Bill C-51 focused on increasing legislative authorities for those regulating drugs, now called ‘therapeutic products’, shifting assessment criteria to a risk-benefit analysis, and putting in place measures which require the continuous provision of health information.⁵⁹⁵ While not encompassing all of the provisions of the life-cycle model which would eventually be found in a modernized Food and Drug Regulation, it did structure the legislative authorities that would be in place for enacting this regime.

The stated objectives of the proposed new Food and Drug Act were “protecting, promoting and improving human health” through “a continued commitment to the health and safety of the public”.⁵⁹⁶ This will require the “ongoing assessment of information about a therapeutic product over its life-cycle... both before and after it reaches the market in order to support its safe use”⁵⁹⁷ through “the assessment of benefits and risks...based on sound scientific and objective evidence”.⁵⁹⁸ That said, the preamble is also careful to indicate that “a lack of full scientific certainty is not to be used as a reason for postponing measures that prevent adverse effects on human health if those effects could be serious or irreversible”.⁵⁹⁹ It is presumed that these measures would include both the approval of a therapeutic product and its removal from the market.

The most substantial changes to drug approvals proposed by Bill C-51 are located

⁵⁹⁴*C-51, supra* note 545.

⁵⁹⁵*Ibid.* at s. 18.7-19.9.

⁵⁹⁶*Ibid.* at preamble.

⁵⁹⁷*Ibid.*

⁵⁹⁸*Ibid.*

⁵⁹⁹*Ibid.*

in sections 18.7 through 20.3, related to authorizations and licenses. Rather than seeking a notice of compliance (NOC), applicants now must seek a market authorization.⁶⁰⁰

Approval of the market authorization will be provided when, on application:

the Minister is of the opinion that the person has established that the benefits that are associated with the therapeutic product outweigh the risks.⁶⁰¹

Additional to the issuance of a market authorization, the Minister may deem a new market authorization to be “subject to terms and conditions that are prescribed from time to time”⁶⁰² and “issue the market authorization subject to the additional terms and conditions that he or she considers appropriate”.⁶⁰³ Unlike the conditions imposed on applicants currently receiving a Notice of Compliance with Conditions (NOCc), applicants now have a statutory obligation to meet the imposed condition. Under s.18.7 (4), applicants “shall comply the terms and conditions to which the authorization is subject”.⁶⁰⁴

Incorporated within these sections are the powers for conducting a risk-benefit analysis of new drugs (therapeutic products) superseding the regulatory provisions currently captured in Division 8 of the *Food and Drug Regulations*.⁶⁰⁵ Likewise, the provisions of s.18.7 that allow for the approval of a market authorization with conditions and the obligation to meet these conditions, allow for the licensing of products with continued obligation to provide safety and efficacy data (i.e., pharmacovigilence). Under

⁶⁰⁰C-51, *supra* note 544 at s. 18.7(1).

⁶⁰¹*Ibid.*

⁶⁰²*Ibid.* at s. 18.7(2)

⁶⁰³*Ibid.* at s. 18.7(3).

⁶⁰⁴*Ibid.* at s. 18.7(4).

⁶⁰⁵FDAR, *supra* note 71.

s.18.9, the Minister may on his or her own initiative “amend a market authorization or the terms and conditions to which it is subject”.⁶⁰⁶

Section 19(1)(c) would allow for the suspension or revocation of a market authorization where the applicant violates the Act, a term, or condition, or “the risks that are associated with the therapeutic product to which the authorization relates [or are later identified to] outweigh the benefits”.⁶⁰⁷ The Minister is expected to first give the market authorization holder an opportunity to ‘make representations’ in response to the planned revocation or suspension. Yet in the case of a suspension it should not be delayed “to respond to a serious and imminent risk of injury to health”.⁶⁰⁸ Section 24(1), similarly, allows for compelling a manufacturer to recall a product which “presents a serious or imminent risk of injury to health”.⁶⁰⁹

These provisions are given a little more weight because applicants can now be compelled to “provide the Minister with the information that is in their control and that the Minister considers necessary for the administration of this Act”.⁶¹⁰ This includes “information that is in the person’s control and that is necessary for the Minister to determine whether it presents that risk”.⁶¹¹ This would include information related to ongoing or discontinued clinical trials,⁶¹² which would enable managers to reassess clinical evidence related to the product’s safety and efficacy. Linked to these provisions

⁶⁰⁶*C-51*, *supra* note 544 at s. 18.9(1).

⁶⁰⁷*Ibid.* at s. 19(1)(c)

⁶⁰⁸*Ibid.* at s. 19.1(2)

⁶⁰⁹*Ibid.* at s. 24(1).

⁶¹⁰*Ibid.* at s. 20.6.

⁶¹¹*Ibid.* at s. 20.5.

⁶¹²*Ibid.* at s. 20.

are increased powers for Health Canada inspectors to enforce the provisions of the Bill⁶¹³ and penalties for contraventions of the Bill.⁶¹⁴

Bill C-51 did not become law before the 30th Parliament was prorogued on September 7, 2008.⁶¹⁵ Prior to the Bill falling off the order table, the Conservative Government announced several proposed changes that they intended to introduce. In response to a high level of criticism that was received in relation to how the Bill would impact natural health products, it was announced that all measures within the Act would now “depend on the nature of the product and its intended use”.⁶¹⁶ The proposed new prologue would include a statement to the effect that:

the information required to demonstrate that a therapeutic product’s benefits outweigh its risks depends on the nature of the product and its intended use; and that the risk of injury to health is a factor to taking administrative and enforcement measures.⁶¹⁷

Risk and the Life-Cycle Model

Whatever form the new *Food and Drug Act* adopts, it is clear that central to the underlying life-cycle model will be the concept of risk, conceived in terms of the counterbalance in risk-benefit analysis, and in terms of the regulatory intervention that is required based on the nature of the product.⁶¹⁸ Yet quantifying this risk and giving it

⁶¹³*Ibid.* at s. 23 to s. 28

⁶¹⁴*Ibid.* at s. 31 to s. 36.

⁶¹⁵Although, no legislative activity has been undertaken in relation to a revised *Food and Drug Act* since September 2008, the *Health Canada - Report on Plans and Priorities* indicates that modernization of the drug regulatory system and corresponding Act continue apace, see Health Canada, *Health Canada - Report on Plans and Priorities* (2010-11) (Ottawa: Health Canada, 2009), online: <<http://www.tbs-sct.gc.ca/ppg-cpr/so-rs-eng.aspx?Rt=1041&Pa=0&Gc=0&So=8231&Dt=4>> [2010 RPP]

⁶¹⁶See, *C-51 Summary*, *supra* note 547 at page 12.

⁶¹⁷*Ibid.*

⁶¹⁸*Ibid.*

formal meaning is no easy task, and the form and measure that Health Canada gives to risk (and benefits for that matter) will have far-reaching implications for health and safety. As with any regulatory tool, risk-benefit analysis and risk measurement can be adopted appropriately or inappropriately. Employed correctly, it is an effectual measure for quantifying and documenting those criteria upon which decisions are based; employed incorrectly, it can allow for questionable decision-making.

An essential element of the progressive licensing model will be flexible departure from the standard requirements of approval when an urgent need is identified. PL has defined flexible departure as:

Deviation from the standard baseline requirement for evidence supporting a drug's efficacy and safety that is necessary for the drug to attain initial market authorization. There must be a compelling reason justifying such a departure from baseline standards.⁶¹⁹

In effect, this would allow the granting of a license when there are extraordinary circumstances. How a compelling reason will be determined and how the risk-benefit assessment for products will vary during flexible departure remains to be determined. As one author has suggested:

To 'depart' from the baseline means that while a positive benefit-risk profile for the particular pharmaceutical product constitutes an important element of the standard for approval, other important 'contextual' evidence may counterbalance and offset the requirements of substantial safety and efficacy evidence.⁶²⁰

What other contextual factors will play a role in risk assessment leading to flexible departure remains a very large question. Some authors have already raised the potential fear that:

⁶¹⁹*PL Website, supra* note 352 at Glossary.

⁶²⁰*Bouchard, supra* note 440.

Health Canada is proposing to lower the threshold for initial market authorization licenses in exchange for additional safety and efficacy studies as a condition for continuing to sell a drug⁶²¹

Other authors argue that the inclusion of reasonable health and safety considerations (in particular, increased access to urgently needed drugs) is a path down which Health Canada has already started⁶²² and that regulators are unlikely to use benefit-risk assessment or flexible departure for “regulatory risk-taking”⁶²³ with new products. Teasing out the intent and implications of shifting to a risk-benefit model is an essential step in evaluating the proposed new life-cycle model.

(a) Whither Risk-Benefit Analysis

The shift to connecting regulatory activity and regulatory interventions to measurements and interventions based on risk is part of a general trend in Canadian governance which is shifting toward “advancing the efficiency and effectiveness of regulation by ascertaining that the benefits of regulation justify the costs”.⁶²⁴ In the health context this has meant a shift toward ensuring that regulatory interventions are based on sound risk-assessment principles and “focusing human and financial resources where they can do the most good, and by demonstrating tangible results”.⁶²⁵ This is to be done by assuring that decisions are made “based on evidence and the best available knowledge

⁶²¹W. Kondro, “Health Canada Proposes New Regulatory Regime for Drugs” (2007) 176(9) *CMAJ*, (PUBMED).

⁶²²*Sawicka, supra* note 445.

⁶²³*Bouchard, supra* note 440.

⁶²⁴Government of Canada, Treasury Board of Canada Secretariat, *Cabinet Directive on Streamlining Regulations* (Ottawa: Treasury Board of Canada Secretariat, 2007), online: <<http://www.tbs-sct.gc.ca/ri-qr/directive/directive00-eng.asp>>, [CDSR].

⁶²⁵*Ibid.*

and science”.⁶²⁶ Decisions are to be based on quantifiable measures of cost and benefit, or in the case of health, on particular assessments about potential risk and benefit.

(b) Cost-Benefit Analysis

Risk assessment is a branch of a wider field of regulatory-economic valuation called cost-benefit analysis. Traditionally, cost-benefit analysis is an analytic procedure which estimates the net economic value of a given policy or project. It converts all costs and benefits into a monetary metric and measures whether the benefits outweigh the costs.⁶²⁷ Under cost-benefit analysis, all regulatory procedures should be subject to a quantified analysis of the benefits and cost that flow from their implementation. Those regulations that do not pass a cost-benefit analysis “should be struck down, not enacted, or at least undergo some further process of scrutiny”.⁶²⁸

Cost-benefit analysis first emerged as a regulatory tool in dealing with large environmental projects in the United States and United Kingdom.⁶²⁹ It was adopted from investment modeling, where before any investment could be undertaken, its benefits (in monetary terms) should exceed its costs (in monetary terms). For environmental projects, it became a decision that any long-term benefits (in terms of government expenditures) should outweigh the costs (in terms of government expenditures).⁶³⁰ Initially, this was

⁶²⁶*Ibid.*

⁶²⁷*Ibid.*

⁶²⁸*Ibid.*

⁶²⁹D. Pearce, “Cost Benefit Analysis in Environmental Policy” (1998) 14(4) *Oxf. Rev. Econ. Policy*, 84 (HEINONLINE).

⁶³⁰*Ibid.*

related to the allocation of scarce resources, but gradually it began to be quantified in terms of the value and cost that these projects could have to long-term human health and environmental safety.⁶³¹ This required an increase in methods for quantifying the value and costs to human health.

In the 1980s, under Ronald Reagan in the United States and under Margaret Thatcher in the United Kingdom, cost-benefit modeling for regulatory activity became tied into concepts of “eliminating waste and promoting efficiency in government [and] reducing [perceived] overregulation”.⁶³² The basic idea was that all government activity should be measured in quantifiable activities such that it “is well managed and accountable and that resources [should be] allocated to achieve results”.⁶³³ As one author has noted:

Before the 1980s, public health and environmental policies were debated primarily on scientific, ethical and legal grounds, with less emphasis on costs – let alone monetized benefits. More recently, it has become the norm to assume the need for cost-benefit analysis of new policies, comparing monetary costs and estimates of the monetary value of benefits. Just as business should only make an investment if the expected revenues exceed costs, the new approach suggests that government should only adopt a new initiative if its expected benefits exceed its costs.⁶³⁴

⁶³¹D. Pearce, “The Limits of Cost Benefit Analysis as a Guide to Environmental Policy” (1976) 29(1) *Kylos* 97 (LEXIS)

⁶³²F. Ackerman, “Critique of Cost-Benefit Analysis, and Alternative Approaches to Decision-making: A Report to Friends of the Earth England, Wales and Northern Ireland” (Medford, Massachusetts: Global Development and Environment Institute, Tufts University, 2008) online: <http://www.ase.tufts.edu/gdae/Pubs/rp/Ack_UK_CBACritique.pdf>, [Ackerman].

⁶³³Government of Canada, Treasury Board of Canada Secretariat, *The Programs and Activities of the Secretariat* (Ottawa: Treasury Board of Canada Secretariat, 2009), online: <<http://www.tbs-sct.gc.ca/tbs-sct/abu-ans/tbs-sct/paa-aap-eng.asp>>, accessed July 20, 2010.

⁶³⁴Ackerman, *supra* note 632 at page 1.

(c) *Risk-Benefit Assessment*

Traditional risk assessment is a subset of cost-benefit analysis focused on evaluating the health or environmental risks that are associated with a particular hazard.⁶³⁵ More specifically, it is a “set of techniques for quantifying the morbidity, fatalities or fatality risks resulting from various hazards”.⁶³⁶ It is a method for identifying the potential dangers associated with a given hazard and in turn identifying those benefits (and methods for mitigation) which would result from exposing the public to that hazard.

As one author suggests:

Estimating the benefits and costs of risk-reducing regulations (requires, inter alia) a risk assessment that ...characterizes the probabilities of occurrences and outcomes of interest ...[T]he risk assessment should generate a credible, objective, realistic, and scientifically balanced analysis; present information on hazard, dose-response, and exposure (or analogous materials for non-health assessments), and explain the confidence in each assessment.⁶³⁷

For drugs this means balancing the health and social benefits that would result from access, versus the dangers that may result from access. As with all hazards, this will involve detailed characterization and projection as to the nature and structure of these hazards.

The keynote publication for government risk assessment was the 1983 *Red Book* published by the U.S. Environmental Protection Agency (EPA) to assist in toxic risk

⁶³⁵Government of the United States of America, National Research Council, Committee on the Institutional Means for Assessment of Risks to Public Health, *Risk Assessment in the Federal Government: Managing the Process* (Washington: National Academy Press, 1983), [Red Book].

⁶³⁶*Ibid.*

⁶³⁷C. J. L. Murray & A. D. Lopez, “On the Comparable Quantification of Health Risks: Lessons from the Global Burden of Disease Study” (1999) 10(5) *Epidemiology* 594 (PUBMED) [Lessons].

assessment.⁶³⁸ The model proposed in the *Red Book* envisioned four stages in a toxic risk assessment: (i) hazard assessment, (ii) dose-response assessment, (iii) exposure assessment and (iv) risk characterization. The first involves the establishment of toxicity and a causal link to harm. The second seeks to quantify that toxicity in relation to human physiological harm. The third quantifies the likely extent of that harm's impact on the population. The final stage involves characterizing the effect of the combined toxicity and likely exposure as an overall impact against "the result[s] of various regulatory interventions".⁶³⁹ While the *Red Book* model is no longer commonly employed, its methodological steps of identifying a risk, measuring and evaluating the risk, gauging the extent of impact of that risk and then weighing them against various options still forms the basis of most risk assessment.

(i) *The Health Canada Decision-Making Framework (DMF)*

Health Canada has incorporated many of the elements of risk-benefit analysis and cost-benefit analysis into its own core policy for dealing with health risks. The *Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks*⁶⁴⁰ (DMF) is a tool to "improve the effectiveness of the risk management decision-making process".⁶⁴¹ It serves as a cohesive "tool which formalizes decision-making as a consistent process with identifiable steps...to [assure] important principles and

⁶³⁸*Red Book*, *supra* note 635.

⁶³⁹*Lessons*, *supra* note 6 at 631.

⁶⁴⁰Health Canada, *Health Canada Decision- Making Framework for Identifying, Assessing, and managing Health Risks* (Ottawa: Health Canada, 2000), online: <http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/risk-risques_tc-tm-eng.php>, [DMF].

⁶⁴¹*Ibid.*

organizational values of decision-making”.⁶⁴² Initially adopted as a tool for assessing the health hazards of specific agents, the DMF has become a central tool to guide all Health Canada “policy development and decision-making”.⁶⁴³

Evolved from the simple *Red Book* model, the DMF follows the same steps of issue identification, quantification, priority setting, and strategy selection. The first stage of the DMF is identifying the issue and the context, which basically involves collecting and analyzing information on “the agent(s) underlying the issue; the adverse consequences associated with the agent(s); susceptible populations; exposure to the agent(s); and the scientific uncertainties that exist”.⁶⁴⁴ Next is the formal assessment of risks and benefits, which involves assessing, quantifying, and characterizing the risks and benefits (discussed in greater detail below). The next step is identifying and analyzing options, based on “a range of risk management options”.⁶⁴⁵ Next is the selection of the most appropriate mitigation strategy. The final step is implementing the strategy and instituting measures to ensure that the strategies adopted are effective.

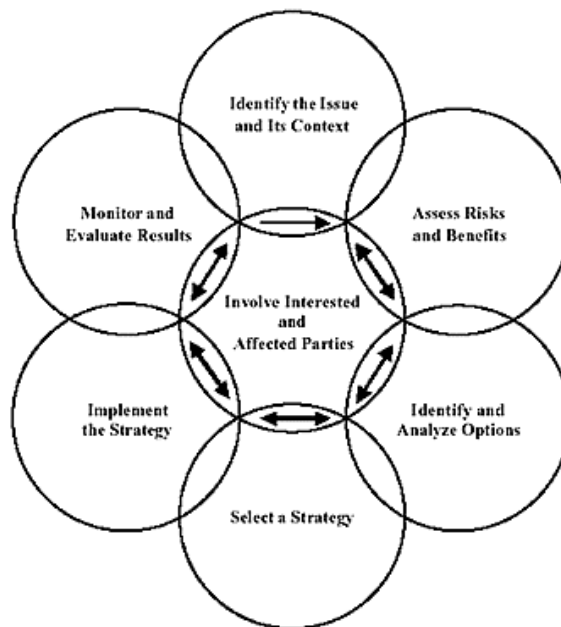
⁶⁴²*Ibid.*

⁶⁴³*Ibid.* at 5.

⁶⁴⁴*Ibid.* at 16.

⁶⁴⁵*Ibid.*

Figure 2: The Health Canada Decision-Making Framework⁶⁴⁶ (DMF)



It is more than coincidental that the DMF model can easily be mapped onto the Progressive Licensing model. Both are basically a feedback loop based on initial issue characterization and health risk assessment, selection of an option, and modification of practice based on increased knowledge. The Progressive Licensing model is likely an attempt to adapt the DMF to drug licensing, employing many of the same risk and benefit considerations with the addition of pharmacovigilance as the monitoring and evaluation tool. Yet a crucial question still remains: what criteria will be considered in formulating the risk and benefit of any new drug?

(ii) Defining Risks

Looking at the DMF, we gain insight into many of the risk assessment practices

⁶⁴⁶*Ibid.*

and tools that are likely to be used by Health Canada (TPD) in formulating any risk assessment of a new drug. At its most basic, risk will be established by (1) identifying the potential hazards, (2) characterizing these hazards and (3) assessing the likely effect on the population (size of the exposure to the hazards).

Taking the DMF as a starting point, we can identify some elements that are likely to be considered in formulating risks for a cost-benefit analysis of a health issue. The first consideration is that any harm will be weighed by the severity of the potential harms (how harmful it is) and the extent to which the harm affects the population (extent of exposure).⁶⁴⁷ Under the DMF, the first consideration is called characterizing the hazards and involves “qualitatively and/or quantitatively evaluating the adverse health effect(s) that humans may experience under expected levels of exposure to the agent(s) under study”.⁶⁴⁸ The second consideration is called exposure assessment, which is “a process used to develop a qualitative and/or quantitative estimate of the magnitude, frequency, duration, route and extent of human exposure to an agent”.⁶⁴⁹

Under the DMF, hazard or risk characterization is focused on “physical health effects, and have relied on data from toxicology and epidemiology studies and in some cases, from surveillance”. The first phase of risk characterization involves identifying hazards and under the DMF includes a very specific collection of steps:

1. identifying the agent(s) causing the adverse health effect(s); collecting relevant scientific data; determining the relative weight of studies having

⁶⁴⁷*Ibid.*

⁶⁴⁸*Ibid.* at 29.

⁶⁴⁹*Ibid.* at 30.

- different results; determining the relative weight of different types of studies (e.g. epidemiology, toxicology);
2. examination of the scientific data for evidence of a relationship between the agent(s) and the adverse health effect(s);
 3. identifying the mode and mechanism of action of the agent(s);
 4. identifying those dose levels that are, and are not, associated with adverse health effects (e.g. for toxicology studies, No Observed Adverse Effect Levels [NOAELs] or Lowest Observed Adverse Effect Levels [LOAELs]);
 5. determining the critical effects associated with exposure to the agent;
 6. determining the significance of a positive finding in studies having different routes of exposure compared to the population(s) at risk;
 7. deciding if the studies have any data limitations that might affect their interpretation or invalidate their results;
 8. for nonhuman studies, ensuring that adequate protocols, a sufficient number of animals, and appropriate dose levels have been used, and determining how different metabolic pathways or rates should be considered;
 9. considering sources of uncertainty and other limitations, and how may these impact upon the hazard identification;
 10. deciding the overall weight of evidence taking into account the quality of the data; and
 11. identifying the hazard(s) of concern.⁶⁵⁰

For new drugs, this would involve focusing on the industry-submitted monograph data on safety, efficacy, and quality, and identifying any potential risks that are identified or implied in this data. It likely involves a degree of speculation and/or extrapolation by drug reviewers to identify the various elements of risk that a drug could hypothetically pose. According to the TPD's own *Standing Operating Procedure: Using the Pharmaceutical Safety and Efficacy Assessment Templates (PSEATs) to Prepare Reports*

⁶⁵⁰*Ibid.* at 28-29.

on *Submissions for Marketing Authorizations*,⁶⁵¹ presently the following factors will be taken into consideration by reviewers when estimating a product's risk:

1. pre-clinical toxic dose levels relative to proposed maximum human dose, taking into account toxic kinetic differences
2. adverse events in target population
3. adverse events in subpopulations
4. potential for drug interactions
5. other potential safety concerns (e.g. QT interval prolongation)
6. risk of abuse or misuse
7. information outside the submitted dossier (e.g. expert advice, medical literature, foreign regulatory bodies)⁶⁵²

According to the DMF, considering these factors “requires judgment [and] depends upon conducting a systematic analysis that.... carefully considers scientific uncertainties, related assumptions, and potential impacts”.⁶⁵³

In formulating this risk characterization, the DMF indicates a very set series of steps. The first is a quantitative estimation of the risk. This begins with a review of all relevant information available related to the specific hazard. This will involve “examining, summarizing, and integrating”⁶⁵⁴ available information and considering “the quality, completeness and relevance of [available] information”.⁶⁵⁵ The PSEAT guideline outlines very detailed steps for reviewing the technical information in clinical and non-clinical studies. Next is the generation of a quantitative estimation of risk, to ensure that decisions are “based on careful analysis of the weight of scientific evidence that supports

⁶⁵¹Health Canada, *Standing Operating Procedure: Using the Pharmaceutical Safety and Efficacy Assessment Templates (PSEATs) to Prepare Reports on Submissions for Marketing Authorization* (Ottawa: Health Canada, 2006), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/proj/practice-pratique/grp_bpe_procedure-eng.php#appen5>, [PSEAT].

⁶⁵²*Ibid.*

⁶⁵³*DMF*, *supra* note 640, at 32.

⁶⁵⁴*Ibid.* at 34

⁶⁵⁵*Ibid.*

conclusions about the risks”.⁶⁵⁶ Again, the PSEAT guideline provides detailed guidance on how studies should be weighed and quantified for their evidential merit. The next step is a qualitative estimation of the uncertainties that involves a description of “major sources of uncertainty and alternative views”.⁶⁵⁷ Risks are then prioritized or compared to “determine priority for action”⁶⁵⁸ and to “estimate the significance (or severity) of the health effects”.⁶⁵⁹ Finally, there is a weighing of the “scientific evidence, in a qualitative way, [in] order to determine whether there is support for the conclusion about risk”.⁶⁶⁰

⁶⁵⁶*PSEAT*, *supra* note 651.

⁶⁵⁷*Ibid.*

⁶⁵⁸*Ibid.*

⁶⁵⁹*Ibid.*

⁶⁶⁰*Ibid.*

(iii) Uncertainty and Risk

The process for risk characterization above shows a gradual shift from empirical and quantitative risk identification to a more qualitative risk measurement. What starts off as a rather quantified exercise of risk measurement becomes a qualitative estimation of the uncertainties of risks. As the DMF identifies, these sources of uncertainty may result from many sources:

Uncertainties may result from: the limited availability of scientific data on for example, exposure or intake rates; long time delays between exposure and effect; the need to extrapolate data to predict the health consequences of human exposures; difficulties in determining appropriate mathematical models for extrapolation; simultaneous exposures to a variety of different agents (making it difficult to determine the effects of a single agent); and judgments made at each step of the process.⁶⁶¹

In assessing the information, Health Canada scientists will be called on to “make inferences, assumptions, and judgments”⁶⁶² in order to characterize the risks.

Estimating the risk of uncertainties is in no way systematic or quantitative. While the PSEAT does discuss listing the undetermined information flowing from submitted data, it does not generally ask reviewers to produce a qualitative measure of unknown health risks, or as the DMF suggests, a subjective “summary of the uncertainties that have been noted throughout the risk assessment process, and explaining the potential impact of the uncertainties on the risk estimates in a non-technical manner”.⁶⁶³ Moving from a precautionary approach based on an SEQ standard would involve the introduction of qualitative measures of uncertainty.

⁶⁶¹*DMF*, *supra* note 640 at 34.

⁶⁶²*Ibid.*

⁶⁶³*Ibid.* at 35.

A whole science has emerged for the estimation and identification of these uncertainties (Uncertainty Analysis),⁶⁶⁴ yet ultimately it remains a speculative exercise, one that is more often than not predicated on existing patterns (what is known) and assumes uniformity amongst unknown risks (what is unknown). This is a very clever trick of logic, since the ultimate truth of most unknown risks is that they will vary from an existing pattern, and it is for that reason that they cannot be foreseen or known prior to their occurrence.

Generating these subjective estimations of uncertainty “can strongly be affected by the social, cultural and institutional context of a decision”.⁶⁶⁵ This qualitative identification of unknowns or uncertainties represents potentially the greatest weakness in all risk characterization. The DMF itself acknowledges that “numerical estimations of risk can give the misimpression of precision, be easily misinterpreted and be misused in the absence of information which puts them into context”.⁶⁶⁶

The existing approach to drug review has been precautionary where there is excessive uncertainty relating to safety, efficacy, or quality, or as the DMF asserts, it “treats the concept of precaution as pervasive”.⁶⁶⁷ This has meant that in those cases where judgment of uncertainties is not comprehensive, there has been a “need to take

⁶⁶⁴M. G. Morgan, M. Henrion & M. Small, *Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis* (Cambridge: Cambridge University Press, 1990), see also Ackerman, *supra* note 632.

⁶⁶⁵Government of the United States of America, National Research Council, Committee on Risk Characterization, *Understanding Risk: Informing decisions in a Democratic Society* (Washington: National Academies Press, 1996), at page 116.

⁶⁶⁶DMF, *supra* note 640, page 35.

⁶⁶⁷*Ibid.* at 8.

timely and appropriately preventative action, even in the absence of a full scientific demonstration of cause and effect”.⁶⁶⁸ Previously, regulators had tended to be conservative in their request for proof of the SEQ standard, and asked for the burden to be on manufacturers to prove through demonstrated scientific research any uncertainties related to a product’s SEQ.⁶⁶⁹ Yet this approach to uncertainty and the licensing of a new drug seems to be changing, as the preamble to Bill C-51 asserts: “a lack of full scientific certainty is not to be used as a reason for postponing measures that prevent adverse effects on human health if those effects could be serious or irreversible”.⁶⁷⁰ Quantitatively addressing pressing issues of uncertainty may no longer be the key elements in a drug assessor’s risk-benefit analysis; a host of qualitative and subjective data may come to dominate a drug’s risk and benefits.

(iv) Defining Benefits

Defining the benefits of a new drug can be more problematic than defining the risks of a given product. Any new drug has a host of potential benefits that include the obvious therapeutic merit, but as discussed in previous chapters, they may also include

⁶⁶⁸See *FDAR*, *supra* note 71.

⁶⁶⁹See *PSEAT*, *supra* note 651.

TPD Activities required to address uncertainty related to SEQ. Potential safety (and other) issues arising from the non-clinical studies that may have implications for clinical use:

(i) limitations of the non-clinical studies in predicting potential adverse effects in humans for this indication; (ii) issues highlighted in the quality (chemistry and manufacturing) review that may affect the reliability of the non-clinical data; (iii) absence of mandatory or scientifically prudent studies (e.g. carcinogenicity) and deviations from expected selection of species/systems, study parameters or other deficiencies in methodology (refer to TPD recognized guidelines); (iv) if information outside the submitted studies (e.g. foreign review reports, Scientific Advisory Committees) was accessed, describe its impact on the evaluation of the non-clinical findings; (v) if not discussed in the relevant sections, outline any concerns/issues that were addressed to the sponsor in clarifaxes; (vi) identify findings that need to be reflected in the PM.

⁶⁷⁰*Bill C-51*, *supra* note 544, at Peamble.

innovation that results from the drug patent and the meeting of patient demands. Even the DMF is rather unclear as to what would be considered a health benefit, but asserts that they include both “direct health benefits (e.g. relief of symptoms), or indirect health benefits (e.g. economic, social, or cultural impacts)”.⁶⁷¹ The *PSEAT*⁶⁷² indicates that the following considerations should be taken into account when weighing a drug’s direct benefit:

1. strength of evidence to support proposed dose in target population
2. strength of efficacy in subpopulations
3. information outside the submitted dossier (e.g. expert advice, medical literature, foreign regulatory bodies).⁶⁷³

These benefits will also largely be a qualitative assessment and undertaken only “when it is difficult or impossible for consumers to judge the benefits associated with exposure to an agent and to compare them with associated risks”.⁶⁷⁴

Quixotically, according to the DMF, this assessment “should be done using a societal perspective”⁶⁷⁵ and “technical specialists [in this case, economists] play the lead role in benefit assessment and in making risk-benefit comparisons”.⁶⁷⁶ Scientists are expected to provide evidence for technical issues and “provide guidance in the use of risk assessment results in risk-benefit comparisons and flag additional risk information needs”.⁶⁷⁷ For new drug reviews, this means analyses of “the adequacy of the data and methods used for the analyses, as well as whether the analyses have addressed the

⁶⁷¹*DMF*, *supra* note 640, page 35.

⁶⁷²*PSEAT*, *supra* note 651.

⁶⁷³*Ibid.*

⁶⁷⁴*DMF*, *supra* note 640 at page 37

⁶⁷⁵*Ibid.* at 38.

⁶⁷⁶*Ibid.*

⁶⁷⁷*Ibid.*

appropriate concerns”.⁶⁷⁸ Yet as the DMF notes, benefit must be characterized and “may include direct health benefits (e.g. relief of disease symptoms), or indirect health benefit (e.g. economic, social, or cultural impacts)”.⁶⁷⁹

The DMF identifies the following steps in benefit identification:

1. identify the type(s) of benefits to be examined;
2. identify the measures to be used;
3. collect and analyze the benefit information;
4. determine how to deal with uncertainty; and
5. summarize the benefit information.⁶⁸⁰

The first step in the process involves “identifying the types of benefits examined”.⁶⁸¹

While we have tended to limit benefits to the traditional SEQ standard, as noted above, there is nothing to preclude additional factors such as economic, social, and cultural impacts. These may in turn be measured not only through a drug’s therapeutic merit, but also “effectiveness, efficiency, quality of life, dollar values”.⁶⁸² In relation to government activity as a whole, the net benefit of action has been characterized as:

the potential positive and negative economic, environmental, and social impacts on Canadians, business, and government of the proposed regulation and its feasible alternatives; and how the positive and negative impacts may be distributed across various affected parties, sectors of the economy, and regions of Canada.⁶⁸³

While PLF has articulated that the new life-cycle model will only include health

⁶⁷⁸*Ibid.* at 39.

⁶⁷⁹*Ibid.*

⁶⁸⁰*Ibid.* at 38.

⁶⁸¹*Ibid.*

⁶⁸²*CDSR, supra* note 624.

⁶⁸³*Ibid.*

considerations⁶⁸⁴, the government's own approach to risk assessment has tended to indicate that they consider benefits globally to include a whole broader range of considerations.⁶⁸⁵

At the end of the process, the benefit assessment resolves itself down to a subjective exercise of identifying and accessing the uncertainties related to benefits. In the cases of most new drugs, the benefits are fairly well characterized in the clinical data that is provided with the NDS. Likewise, there is often extensive pressure from patient groups, industry, and interested researchers that backs the significant financial investments that have guided a pharmaceutical drug out of the pipeline.⁶⁸⁶ There is a tendency to see the uncertainties of benefits as far more certain, rather than to project danger to the unknowns of potential risks. As noted in the previous chapter, there is a policy trend to include increasingly opaque monetized benefits such as “innovation” and economic spin resulting from patented activities.

(d) Good Risk-Benefit Analysis – Bad Risk-Benefit Analysis

Overall, risk-benefit analysis has great potential to assist in assessing new drugs, yet it must be applied cautiously. As Avorn has noted:

It's easy to see how a quantitative method that claims to be both objective and fair could seem to provide a neat road map out of the conceptual swamp of subjective clinical judgment. A by-the-number approach to balancing risks and benefits can seem particularly attractive as a

⁶⁸⁴PL Website, *supra* note 352.

⁶⁸⁵CDSR, *supra* note 624 and Government of Canada, Treasury Board of Canada Secretariat, *Canadian Cost-Benefit Analysis Guide: Regulatory Proposals* (Ottawa: Treasury Board of Canada Secretariat, 2007), online: <<http://www.tbs-sct.gc.ca/ocg-bcg/index-eng.asp>>, visited on April 15, 2009.

⁶⁸⁶Avorn, *supra* note 34.

replacement for the shriveling professional sovereignty of both physicians and policy-makers.⁶⁸⁷

Risk assessments are not objective, scientific methodology; they are “literally, uncertain knowledge claims – impressionistic guesses, informed estimation, and probabilistic predictions about a future that cannot fully be known”.⁶⁸⁸ Yet they have the appearance of objectivity and can shield policy-makers’ decisions with objectivity. It is not surprising then, that, as Avorn notes:

the task of assigning values to clinical conditions often embodies a set of hidden assumptions – about methods, about values – that can sometimes distort the supposedly objective recommendations that flow from these methods.⁶⁸⁹

The SEQ standard cannot be abandoned in favour of non-clinical measures of benefit, or underestimations of risk. The more that risk-benefit analysis moves away from quantitative measures (SEQ) into qualitative or speculative measures (uncertainty), the more it can become “automatic and self validating”⁶⁹⁰ of policy decisions.

In order to ensure that risk-benefit analysis does not become meaningless, it must be careful to temper its own biases and be based in some form of empirical data and measurement. Looking to the environmental realm, Frank Ackerman has identified a number of methodological errors which plague poor risk-benefit analysis, including the tendency to focus on monetized values of risk and benefit, the failure of uncertainty to take account of real world problems, the failure to take into account long-term risks, and the tendency to ignore alternatives and constrained variables in favour of a known and

⁶⁸⁷*Ibid.*

⁶⁸⁸R.V. Ericson & A. Doyle, eds., *Risk and Morality* (Toronto: Toronto University Press, 2003) at 52, [Risk and Morality].

⁶⁸⁹Avorn, *supra* note 34 at

⁶⁹⁰*Risk and Morality*, *supra* note 688 at page 5.

accepted list of risks and benefits.⁶⁹¹

To limit these biases, any cost-benefit analysis must take into account multiple criteria for the analysis, look at a holistic evaluation of costs and benefits, and acknowledge the limits of uncertainty with the use of precaution where uncertainty is prevalent.⁶⁹² For the Progressive Licensing model's conception of risk-benefit analysis to work, it too must ensure that it relies upon accurate quantitative data, acknowledging in those cases where uncertainty is prevalent that a risk-benefit analysis may not be decisive, and limit the variables that are considered at drug approval to those directly related to clinical merit and ultimate effect on the population.

One of the initial hurdles in this regard will be ensuring that risks are appropriately characterized and quantified with scientific information. One of the most recent trends at the Health Protection and Food Branch of Health Canada is towards a Risk Based Approach, or "regulation proportional to risk".⁶⁹³ The basic idea is that under an RBA, regulators:

will take into consideration such elements as the risks associated with various product classes and the availability of supporting evidence for safety, quality and efficacy/health claims.⁶⁹⁴

This is reflected in the proposed new wording to Bill C-51, which states that "information required to demonstrate that a therapeutic product's benefits outweigh its risks depends

⁶⁹¹ *Ackerman, supra* note 632.

⁶⁹² *Ibid.*

⁶⁹³ Health Canada, Natural Health Products Directorate, *Fact Sheet – The New Risk-Based Approach for Natural Health Products*, (Ottawa: Health Canada, 2008), online: <http://www.hc-sc.gc.ca/dhp-mps/pubs/natur/nhpr-rba_erpsn-gbr-eng.php>, visited May 14, 2009.

⁶⁹⁴ *Ibid.*

on the nature of the product and its intended use”.⁶⁹⁵ If the RBA makes assumptions about the relative safety of products or classes of products in the absence of scientific evidence, then there is potential for distortion of those scientific standards brought to bear on a product’s review.

A second hurdle will be ensuring that benefits are not over-estimated as meeting an urgent unmet medical need, i.e. flexible departure. In the United States, such benefits resulted in ‘fast-track’ legislation, allowing the FDA to:

expedite the review of [a] drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition.⁶⁹⁶

The definition of what constitutes ‘a serious or life-threatening condition’ and ‘unmet medical need’ has gradually led to an expansive definition that most drugs meet.⁶⁹⁷ This law has allowed for the erosion of the minimal standards proving drug usefulness.⁶⁹⁸ In most cases, drugs can be approved after only the first or second stage of clinical trials. The result is that the “market [has been] flooded with poorly tested drugs of unknown efficacy”.⁶⁹⁹

A final hurdle will involve making sure those measures of risk and benefit do not become too encompassing and lose sight of the SEQ standard. A trend in health risk assessment has been to monetize the values assigned to health risks and benefits; in the case of risks, to develop measures of the financial cost of adverse drug reactions (through

⁶⁹⁵*C-51 Summary, supra* note 547.

⁶⁹⁶21 U.S.C. 356(a)(1)

⁶⁹⁷*Catch 22 supra* note 139.

⁶⁹⁸US, *Orphan Drug Development Program*, 4 U. S. REG. REP 1-6 (1987).

⁶⁹⁹*Catch 22, supra* note 139 at 137.

individual life valuations), and in the case of benefits, to factor in the market value (and multiplier effect via innovation) of new drugs to the economy as a whole, as if they were any consumer product.⁷⁰⁰ If these variables become criteria in new drug approvals, they will dilute the ultimate safety goal underlying new drug evaluations. Assigning a value to individual lives (presently around \$6 million)⁷⁰¹ allows for assessment of the cost of life against the value of a drug's being on the market (often worth billions).⁷⁰² If such factors dominate risk-benefit assessment for new drugs or drugs already on the market, regulatory intervention would become meaningless and Health Canada would be abrogating its responsibility to protect the health and safety of Canadians.

Pharmacovigilance

The other major element of the new progressive licensing model is pharmacovigilance. Found at the centre of the proposed model, it is designed to supplement the knowledge and information gained by the initial risk assessment with real-world information gained once a product has been released. As has been indicated by Health Canada:

The central concept of Progressive Licensing is that, over time, there is a progression in knowledge about a drug. The emphasis of the new framework is to identify opportunities within this progression over the full life-cycle of a drug, rather than placing the focus primarily upon pre-market assessment.⁷⁰³

Achieving this goal means the establishment of more effective methods for the continual

⁷⁰⁰Government of Canada, Policy Research Initiative, *Economic Valuation of Mortality Risks: Review and Recommendations for Policy and Regulatory Analysis* (Ottawa: Policy Research Initiative, 2009), online: <<http://www.policyresearch.gc.ca>>.

⁷⁰¹*Ibid.*

⁷⁰²*Ibid.*

⁷⁰³*PL Concept Paper, supra* note 58 at page 1.

monitoring and evaluation of licensed drug safety. Planning for post-market surveillance would become an essential part of the pre-market evaluation of a drug. As the *Progressive Licensing Concept Paper* suggests:

Planning for the conduct of post-market activities...would become a required part of the pre-market filing, so that expectations for identifying and managing drug benefits and risks are established ahead of marketing for each drug.⁷⁰⁴

According to the progressive licensing model, the pre-market filing would then “arguably better mirror the actual considerations for licensing a drug ... [including ensuring] a sufficient life-cycle management plan has been filed by the manufacturer to allow for introduction of the drug to the market”.⁷⁰⁵

The extent to which this life-cycle management plan will affect the ultimate decision to license a product (the product’s risk-benefit analysis) is crucial to how the traditional model of SEQ will be affected by pharmacovigilance. Presently there are two emerging international models for how to incorporate risk mitigation management into product approvals. Under the emerging U.S. model, risk mitigation planning (Risk Evaluation and Minimization Strategies) is actively used as a benefit-risk consideration to allow the licensing of products earlier than would be possible under previous SEQ models.⁷⁰⁶ The more conservative EU model requires Risk Management Plans, but these

⁷⁰⁴*Ibid.*

⁷⁰⁵*Ibid.*

⁷⁰⁶*Food and Drug Administration Amendments Act*, 21 U.S.C. 30. 2007. Title IX, [FDAAA], See also Government of the United States of America, Department of Health and Human Services, Food and Drug Administration, *Report to Congress: Changing the Future of Drug Safety: FDA Initiatives to Strengthen and Transform the Drug Safety System* (Washington: Department of Health and Human Services, 2009) [FDA Initiatives] and United States, Institute of Medicine, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Washington: National Academies Press, 2006) [IOM Report], and United States Senate, Committee on Finance, *Report to Congressional Requesters: Drug Safety:*

become a supplemental element that is grafted onto the existing standard of drug safety and efficacy approval.⁷⁰⁷ The ultimate utility and implication that pharmacovigilance has for the new progressive licensing model will largely depend upon which of these two models Canada adopts.

In the following section I will discuss the nature of pharmacovigilance and the competing models of pharmacovigilance that exist in the United States and European Union. This will enable an analysis of how these models are likely to impact upon the proposed new drug regime and suggest which directions may be most appropriate for Canada to adopt under its new progressive licensing regime.

(a) What is Pharmacovigilance?

At its most basic, pharmacovigilance has been defined by the WHO as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”.⁷⁰⁸ Basically, it includes any activities undertaken to monitor the safety and efficacy of a drug post-market. Yet with time, pharmacovigilance has come to mean much more than mere post-market surveillance for adverse drug events. Pre-approval clinical testing “may be sufficient to determine efficacy, [but it] may not be sufficient to detect safety problems, particularly

Improvement Needed in FDA's Postmarket Decision-making and Oversight Process (Washington: Government Accounting Office, 2007) GAO-06-402, online: <<http://www.gao.gov>> [GAO Report].

⁷⁰⁷EC, *EC Regulation 726/2004*, [EC PvP Reg].

⁷⁰⁸*WHO PvP*, *supra* note 555.

those that occur as a result of long-term use”.⁷⁰⁹

With time, pharmacovigilance has also become an umbrella term for the entire field of activities, often called pharmaco-epidemiology, that can be put in place pre- and post-market to monitor, mitigate, and evaluate the real-world safety and efficacy of drug products.⁷¹⁰ It has evolved from a system of adverse event reporting and risk communications to a system based on a whole host of tools including risk management plans, risk mitigation plans, secondary markers, and others. Pharmacovigilance planning therefore becomes any “proactive approach to identifying risks associated with a product prior to market authorization, as well as to planning for or implementing means to investigate or mitigate those identified risks”.⁷¹¹

In 2007 the Institutes of Medicine (IOM) in the United States produced a report assessing the overall drug review process in the United States.⁷¹² One of the key findings was that the present model, based primarily on post-market research, was inadequate to reflect the real safety and efficacy profile of products. Post-market reviews were designed to assess a product’s efficacy rather than safety.⁷¹³ Many details about a drug’s safety and patterns of real-world use will only become apparent once a product is on the market, including details such as its effect in combination with other products, how it affects specific sub-populations, the effects of longer-term exposure, the product’s relative

⁷⁰⁹M. Gilhooley, “Addressing Potential Risks: The Limits of Testing, Risk Signals, Preemption and Drug Reform Legislation” (2008) 59 *South Carolina L. R.* 347 at 356 (LEXIS).

⁷¹⁰D. Mann & E. B. Andrews, *Pharmacovigilance* (Etobicoke: John Wiley & Sons Canada Ltd, 2007).

⁷¹¹*PL Website*, *supra* note 352 at Glossary.

⁷¹²*IOM Report*, *supra* note 706.

⁷¹³*Ibid.*

effectiveness in customary practice or use, and low-frequency effects that can only be detected in large populations.⁷¹⁴ All of these observations identify the need to modify the present one point in time regulatory review for “improvements in post-market surveillance and [expanded] authority to require additional post-market trials or observational studies when needed”.⁷¹⁵

(b) The Emergence of Pharmacovigilance

In 1972, the WHO identified the need for greater “post-market” surveillance of pharmaceuticals, and international cooperation in the sharing of information related to post-market safety and efficacy data.⁷¹⁶ In the report *International Drug Monitoring: The Role of National Centers*, the WHO recommended “the development of systems for detecting adverse reactions at both the national and international levels”.⁷¹⁷

Over the next few decades, a patchwork of national methods for the detection, reporting, and sharing of information based primarily on adverse events reports developed.⁷¹⁸ The system which began to emerge was one that required “health care professionals (and consumers in a few countries) to spontaneously report [adverse events]

⁷¹⁴A. Hartzem, H. Tilson & K. Chan, *Pharmacoepidemiology and Therapeutic Risk Management* (Toronto: Harvey Whitney Books Company, 2008) at page 17 [PTRM].

⁷¹⁵M. Gilhooley, “Drug Safety and Commercial Speech: Television Advertisements and Reprints on Off-Label Uses (2010) 47 *San Diego L. Rev.* 357 at 361 (SSRN).

⁷¹⁶World Health Organization, *International Drug Monitoring: The Role of National Centers* (Geneva: WHO Press, 1972).

⁷¹⁷*Ibid.*

⁷¹⁸G. A. Faich, W. Castle & Z. Bankowski, “International Reporting on Adverse Drug Reactions: The CIOMS project. CIOMS ARD Working Group” (1990) 28(4) *Int. J. Clin. Pharmacol. Ther. Toxicol.* 133 (PUBMED).

with drugs”.⁷¹⁹ These methods were hardly uniform, often poorly monitored and evaluated, and varied greatly across national drug regimes.⁷²⁰

The Council for International Organizations of Medical Sciences (CIOMS) produced six working group reports dealing with the post-market surveillance of pharmaceuticals. Beginning with the 1990 report on *International Reporting of Adverse Drug Reaction*,⁷²¹ there were increased calls for the harmonization and standardization of AERs. Progressively the CIOMS reports have provided standards for the recognition, reporting, and sharing of post-market adverse event data, including the 2001 CIOMS V report *Current Challenges in Pharmacovigilance: Pragmatic Approaches*⁷²² which dealt with pharmacovigilance, and the 2005 CIOMS VI document *Management of Safety Information from Clinical Trials*.⁷²³ Adopted to varying degrees by different international regimes around the world, the CIOMS reports were crucial for the ICH and the development of safety regulations in North America, Europe, Japan, and elsewhere.⁷²⁴

Much of this work on post-market drug safety surveillance and setting up the parameters for market drug evaluation began to coalesce in the ICH guidance *E2E*:

⁷¹⁹*Ibid.*

⁷²⁰*Ibid.*

⁷²¹World Health Organization, Council for International Organization of Medical Sciences, *Reporting Adverse Drug Reaction: Definitions of Terms and Criteria for their Use* (Geneva: WHO Press, 1999) [CIOMS].

⁷²²World Health Organization, Council for International Organization of Medical Sciences, *Report of CIOMS Working Group V - Current Challenges in Pharmacovigilance: Pragmatic Approaches* (Geneva: WHO Press, 2001) [CIOMS V].

⁷²³World Health Organization, Council for International Organization of Medical Sciences, *Report of CIOMS Working Group VI – Management of Safety Information from Clinical Trials* (Geneva: WHO Press, 2005) [CIOMS VI].

⁷²⁴B. Coberts, “Chapter 25: Council for International Organizations of Medical Sciences (CIOMS) and CIOMS Report” in B. Coberts, ed. *Manuel of Drug Safety and Pharmacovigilance* 2nd ed. (New York: Jones & Bartlett Learning, 2006).

Pharmacovigilance Planning.⁷²⁵ Overall, the ICH E2E document and CIOMS reports have led to market product evaluations that shift “toward earlier, proactive considerations of risks and potential benefits of drugs in the pre- and peri-approval stages of drug development, leading to a maturing of drug safety”.⁷²⁶

In 2003 the ICH produced guidance document E2E on pharmacovigilance planning.⁷²⁷ E2E highlights specific processes that should be put in place for a pharmacovigilance plan and “describes a method for summarizing the important identified risks of a drug, important missing information, including the potential at-risk populations and situations where the product is likely to be used that have not been studied pre-approval”.⁷²⁸ This planning can then allow for the “benefit-risk balance [to] be improved by reducing risk to patients”⁷²⁹ and “enable information feedback to the users of medicines in a timely manner”.⁷³⁰ E2E provides some broad guidelines for establishment of safety specification, the structure of pharmacovigilance plans, and acceptable pharmacovigilance methods. These include passive surveillance, stimulated reporting, active surveillance, comparative observational studies, targeted clinical investigations, and descriptive studies.⁷³¹ Each of these methods is a mechanism for either increased collection of targeted safety data, or conducting additional post-market surveillance studies.

⁷²⁵*ICH E2E, supra* note 555.

⁷²⁶C. G. Hartford et als., “Pharmacovigilance During the Pre-Approval Phases: An Evolving Pharmaceutical Industry Model in Response to ICH E2E, CIOMS VI , FDA and EMEA/CHMP Risk-Management Guidelines”(2006) 29(8) *Drug Safety* 657 at 657 (HEINONLINE) [Hartford].

⁷²⁷*ICH E2E, supra* note 555.

⁷²⁸*Ibid.*

⁷²⁹*Ibid.*

⁷³⁰*Ibid.*

⁷³¹*Hartford, supra* note 726.

(c) Two Paths for Pharmacovigilance

Pharmacovigilance has two potential implications for new drug approvals. The first is the establishment of tools to ensure the ongoing monitoring of drug safety and efficacy (the life-cycle model). The second is the establishment of mechanisms that enable the mitigation of AERs should they occur. The first would be established by a detailed plan of post-marketing surveillance measures, and in some cases, the establishment of specific conditions for monitoring SEQ at the time of licensing. The second, mitigation, can either be established by measures (conditions of use) put in place on newly licensed products, or by the establishment of risk mitigation strategies to deal with uncertainties.

In effect, pharmacovigilance adds a new variable to the SEQ standard: a pharmacovigilance standard (SEQ and P). The real question becomes how this additional variable will influence the newly introduced risk-benefit analysis. Assuming that a risk-benefit analysis is still largely concerned with establishing a drug's safety, efficacy, and quality, how will the presence of pharmacovigilance plans or pharmacovigilance mitigation strategies affect the risk-benefit profile of a new drug or a promising new therapy under flexible departure? As one author has noted, "more emphasis on post-market safety [may] recalibrate the risk, benefit and uncertainties of therapeutic product development".⁷³² This represents a shift from reliance on pre-market SEQ data to reliance on prospective data generated on SEQ once a product is on the market.

⁷³²*Bouchard, supra* note 440 at 52.

The current mechanism for licensing products with post-market conditions is the Notice of Compliance with Conditions (NOCC). As noted in Chapter 1, an NOC can be issued “to provide earlier market access to potentially life-saving drugs”.⁷³³ Specifically, pursuant to sections C.08.004 and C.08.005 of the FDR, an NOC can be issued for:

promising new drug therapies intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases or conditions for which a) there is no alternative therapy available on the Canadian market or, b) where the new product represents a significant improvement in the benefit/risk profile over existing products.⁷³⁴

In these cases NOCC allows for the approval of drugs that “have demonstrated promising clinical effectiveness in clinical trials”.⁷³⁵ Under these conditions, authorization to market a drug is given “with the condition that the sponsor undertakes additional studies to verify the clinical benefit”.⁷³⁶

Increasingly, NOCC is being used as a mechanism for new drug approvals by Health Canada.⁷³⁷ A recent study which reviewed the conditions of licensing for all new drugs over a seven year period (2001-2008) found that “NOC submissions, which have either the same or less evidentiary requirements as standard submissions with post-market obligations, increased steeply”.⁷³⁸ Specifically, it was found that there has been a gradual shift away from sponsors applying for priority review in favour of NOCC. Yet as analogous studies from the United States suggest, there have been concerns that once they receive marketing, drug manufacturers will fail to meet their post-market

⁷³³See, Health Canada, *Notice of Compliance with Conditions Fact Sheet* (Ottawa: Health Canada, 2005), online: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/nocdfs_accfd-eng.php> [Fact Sheet].

⁷³⁴*FDAR*, *supra* note 71 at s. C.08.004 – s. C.08.005.

⁷³⁵*Fact Sheet*, *supra* note 733.

⁷³⁶*Ibid.*

⁷³⁷*Sawicka*, *supra* note 445.

⁷³⁸*Ibid.* at 2.

commitments.⁷³⁹ This is exacerbated by the fact that the *Food Drug Act*⁷⁴⁰ and *Food and Drug Regulations*⁷⁴¹ as they are currently drafted do not allow for the enforcement of conditions made through a NOC or removal of a marketed drug which fails to meet those conditions.⁷⁴²

The present NOC mechanism is clearly inadequate and pharmacovigilance as articulated under progressive licensing would allow for the marketing of drugs with very prescriptive and enforceable conditions. This can potentially allow for useful therapies which would otherwise not reach the market to become available under very narrow conditions of use, but it can also mean that drugs which have not been sufficiently proven to be safe and effective could also reach the market with inadequate clinical research. The ultimate question becomes how to apply pharmacovigilance in relation to the SEQ standards. Will pharmacovigilance be used as an additional variable in the risk-benefit assessment of new drugs (SEQ+P) or will it be used to mitigate this standard for all promising new therapies (SEQ/P)? In effect, will pharmacovigilance planning be an additional safety variable considered in regulatory approval, or will it become a tool to reduce the pre-market clinical safety data required for approval?

⁷³⁹See, Government of the United States of America, Department of Health and Human Services, Food and Drug Administration, *Report on the Performance of Drug and Biologic Firms in Conducting Post Market Commitment Studies* (Washington: Food and Drug Administration, 2007), 72 Fed. Register 5069 [FDA Post Market]

⁷⁴⁰*FDA*, *supra* note 89.

⁷⁴¹*FDAR*, *supra* note 71.

⁷⁴²See *Bouchard*, *supra* note 440.

(i) The EMEA and US-FDA Experiences with Pharmacovigilance

There are two major regulatory jurisdictions that have already adopted pharmacovigilance measures which can illustrate the outcomes of these two approaches: the European Medicines Agency (EMA) and the United States Food and Drug Administration (US-FDA). Both are early adopters of pharmacovigilance, but each has taken a very different approach to how it influences drug approvals. The lessons learned from these two approaches should ultimately inform how Progressive Licensing decides to implement pharmacovigilance in Canada.

The EMA is responsible for “the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use”⁷⁴³ for all countries within the EU. The EMA’s core mandate is to ease regulatory burdens and duplication between EU countries; “once granted by the European Commission, a centralized (or “Community”) marketing authorization is valid in all European Union States”.⁷⁴⁴ This has meant a trend toward application of uniform standards that can be used by each domestic drug regulatory authority.

The EMA has two documents which lay out the legal requirements for pharmacovigilance within the EU. The first is EC Regulation 726/2004, “laying down Community procedures for the authorization and supervision of medicinal products for

⁷⁴³See EC, European Medicines Agency (EMA), *About Us*, (London: EMA, 2009) online: at: <<http://www.ema.europa.eu>>, accessed May 27, 2009.

⁷⁴⁴*Ibid.*

human and veterinary use”.⁷⁴⁵ In particular, the guidelines set out the procedures that are to be implemented by the EMEA in assessing new drugs for market authorization. The EMEA’s responsibility is to:

Article 57(1)(c) “ensure the safe and effective use of these products, in particular by evaluation, coordination of the implemented pharmacovigilance obligations and the monitoring of such implementation”

Article 57(1)(i) “coordinating the verification of compliance with the principles of good manufacturing practices, good laboratory practices, good clinical practices and the verification of compliance with pharmacovigilance obligations”.⁷⁴⁶

Basically, under the EMEA the responsibility is to ensure that manufacturers have a system of pharmacovigilance in place supplementing safety and efficacy, and to ensure that manufacturers are meeting these obligations. The drug manufacturer’s responsibility is outlined under *Volume 9 A: Guidelines on Pharmacovigilance* 2.1.1 and 2.15⁷⁴⁷ where it is indicated that “a detailed description of pharmacovigilance planning must be included in market authorizations”⁷⁴⁸; packages and manufacturers must guarantee that “an appropriate system of pharmacovigilance [is] in place”.⁷⁴⁹

The EMEA adopts a perspective that pharmacovigilance or pharmacovigilance planning should supplement the SEQ standard (SEQ+P) and not dilute the standard. As one author has noted:

for the European Union, a pharmacovigilance system is not a risk managements system. Details of the pharmacovigilance system must be

⁷⁴⁵EC PvP Reg, *supra* note 707 at preamble.

⁷⁴⁶*Ibid.* at Article 57(1)(c) and (i)

⁷⁴⁷EC, *Volume 9A: Pharmacovigilance for Medicinal Products for Use in Humans* (Geneva: European Commission, 2008), online: <http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm>, [EU 9A].

⁷⁴⁸*Ibid.* at s. 2.1.5

⁷⁴⁹*Ibid.* at s. 2.1.1

supplied with the application for all new market authorizations, while the details of the risk management system are required only in certain circumstances.⁷⁵⁰

EU Risk Management Plans (EU-RMPs) are required when there is a variation to a product's approved status, (i.e. a new active substance, additional risks are identified, a significant change in conditions of use, a request from a competent authority within the EU, or the EMEA identified a safety risk). What pharmacovigilance in the EU is not, is a mechanism to allow for earlier market authorization or authorization of products which have EU-RMPs to be licensed with less SEQ data.

(ii) The United States Food and Drug Administration (US-FDA)

In contrast, the US-FDA has used pharmacovigilance, and in particular mitigation plans, as a tool to allow for the licensing of products with reduced SEQ clinical evidence. As with most international norms, the U.S. has decided to adapt rather than adopt the pharmacovigilance methods identified in ICH E2E⁷⁵¹ and the CIOMS⁷⁵² reports. Directly in response to criticisms raised against the FDA and its post-market safety monitoring,⁷⁵³ the U.S. Congress introduced formal pharmacovigilance activities.⁷⁵⁴

⁷⁵⁰*PTRM, supra* note 714 at page 580.

⁷⁵¹*ICH E2E, supra* note 555.

⁷⁵²*CIOMS, supra* note 721.

⁷⁵³*IOM Report, supra* note 706.

⁷⁵⁴*FDA Initiatives, supra* note 706.

The most recent developments in U.S. drug law are the result of almost two decades of drug reform. In 1992, Congress passed the *Prescription Drug User Fee Act*⁷⁵⁵ (PDUFA) that allowed the FDA to charge drug companies user fees for approvals. PDUFA is subject to renewal every five years, and has meant that the US-FDA has a regular window for updating its legislation and operating mandate.

In 1997, at the first of these renewals, Congress passed the *FDA Modernization Act* (FDAMA).⁷⁵⁶ FDAMA reoriented the FDA's role to "not only prevent the distribution of unsafe products, but also to review and approve new drugs in a timely manner".⁷⁵⁷ Under FDAMA, approval times were shortened, the definition of 'urgent unmet need' was broadened to include 'serious and life threatening need', and outside panels could be contracted to assess drugs on behalf of the FDA.⁷⁵⁸ The resulting fast-track legislation allowed the FDA to:

expedite the review of [a] drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition.⁷⁵⁹

Unfortunately, the definition of a serious or life-threatening condition and unmet medical need has gradually been stretched to include most new drugs.⁷⁶⁰ Vioxx was approved using this fast-track legislation.

In 2007 Congress once again renewed the mandate of PDUFA with the

⁷⁵⁵Pub. L. No. 102-571, 106 Stat.4491 (1992) (codified as amendment at 21 U.S.C. 379 (g-h).

⁷⁵⁶Pub. L. No. 105-115, 111 Stat. 2296 (1997) (codified at 21 U.S.C. 310) [FDAMA].

⁷⁵⁷*Parver, supra* note 384

⁷⁵⁸21 U.S.C. 356(a)(1)

⁷⁵⁹*Ibid.*

⁷⁶⁰*Catch 22, supra* note 139.

*Food and Drug Administration Amendment Act*⁷⁶¹ (FDAAA). The FDAAA introduced a host of changes related to the market authorization and conditions of use of newly approved drugs. One of the largest changes was to *Title IX - Enhanced Authorities Regarding Postmarket Safety of Drugs*.⁷⁶² Much like the intended C-51, *Title IX* gave the US-FDA much greater powers to enforce the imposition of post-market conditions and post-market clinical research.⁷⁶³ For a new drug application, the US-FDA may “require a responsible drug manufacturer to conduct a post-approval clinical trial or trials of the drug, on the basis of scientific data deemed appropriate”.⁷⁶⁴

While not explicitly mentioning pharmacovigilance, under s.905 of the FDAAA the FDA can now impose active “post-market risk identification, analysis, and timelines for reporting”.⁷⁶⁵ Specifically, this can include the “development of post-market risk identification and analysis methods and analysis systems, advanced analysis of drug safety data, and additional clinical trials”.⁷⁶⁶ Unfortunately, the way in which most post-marketing commitments are established by the US-FDA is not through a general post-marketing obligation to conduct pharmacovigilance activities. Instead conditions can only be imposed where “the report and the active post-market risk identification and analysis system [provided by the drug manufacturer] will not be sufficient to meet [post-market monitoring]”.⁷⁶⁷

⁷⁶¹*FDAAA, supra* note 706.

⁷⁶²*Ibid.* at Title IX.

⁷⁶³*Ibid.*

⁷⁶⁴*FDAAA, supra* note 706 s. 901(A)

⁷⁶⁵*Ibid.* at s.905.

⁷⁶⁶*Ibid.*

⁷⁶⁷*Ibid.*, s. 901(D)(i)(ii)

The form this risk identification and analysis system takes is that of a *Risk Evaluation and Mitigation Strategy* (REMS). The US-FDA will ask for REMS where it “determines that a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug”.⁷⁶⁸ The REMS will contain ongoing obligations for “risk evaluation and [a] mitigation strategy”.⁷⁶⁹ The basic idea is that not only does the REMS serve as a plan for post-market safety and effectiveness evaluation, but that it also identifies a plan for minimizing the impact of unknown risks.

The existence of REMS then allows for an abbreviated submission for treatments that address serious or life-threatening conditions and unmet medical needs.⁷⁷⁰ Planning for the minimization of these risks then allows for the shifting of the risk-benefit analysis for these drugs. In effect, the existence of post-marketing risk mitigation strategies and monitoring activities allows for the reduction of SEQ data provided post-market. A recent report to Congress has found that the majority of post-market commitments made in REMS that have led to early licensing have failed to complete the required studies.⁷⁷¹

The unfortunate result is that the U.S. has begun the marketing of “promising therapies” on reduced pre-market safety data.⁷⁷² Often drugs which show some effects at Phase 2 clinical trials will be licensed with a promise to conduct Phase 3 trials once the

⁷⁶⁸ *Ibid.*

⁷⁶⁹ *Ibid.*

⁷⁷⁰ *Ibid.*, s. 501(1)(3).

⁷⁷¹ See *GAO report, supra* note 706.

⁷⁷² *Ibid.*

product is on the market.⁷⁷³ In this case, the promise of pharmacovigilance is used to justify merely creating contingencies to deal with unknown safety and efficacy risks.

Conclusion

(a) Taking the Measure of the Life-Cycle Model

The changes that underlie the life-cycle model hold great promise to resolve many of the problems with current drug regulation in Canada. As has been noted by Lemmens and Bouchard, “the current regulatory process focuses too much on short-term efficacy and safety of drug products [and] there is little control on what happens after a drug is approved”.⁷⁷⁴ Pharmacovigilance should, in theory, increase the requirement for post-market surveillance of new drugs, while risk-benefit analysis could introduce a more balanced appraisal of new drugs. This new regulatory life-cycle, as envisioned in the 2006 Progressive Licensing Framework⁷⁷⁵ (PLF) and Bill C-51,⁷⁷⁶ increases the requirements for ongoing reporting of safety data, gives regulators more powers to enforce post-market conditions and withdraw products, increases the flexibility of the regulator to assess scientific data, and increases the mechanisms for marketing needed new therapies. Yet, this model is also not without its potential pitfalls.

Many authors have been critical of the way in which PLF was developed. As the

⁷⁷³*IOM report, supra* note 706.

⁷⁷⁴T. Lemmens & R. A. Bouchard, “Regulation of Pharmaceuticals in Canada” in J. Downie, T. Caulfield & C. M. Flood, eds., *Canadian Health Law and Policy*, 3rd ed. (Markham: LexisNexis Canada Inc., 2007) at 311 [Lemmens & Bouchard].

⁷⁷⁵*PL Concept Paper, supra* note 58.

⁷⁷⁶*Bill C-51, supra* note 544.

editor-in-chief of the *Canadian Medical Association Journal* (CMAJ) notes, “two voices dominated the change process: the pharmaceutical industry and Health Canada”.⁷⁷⁷ He goes on to argue:

These voices, albeit important, are not the only stakeholders; their focus is far too narrow and potentially self-serving. Canada’s health professionals, experts and the public are nowhere in the picture.⁷⁷⁸

Joel Lexchin has been even more critical, going so far as to state that:

democratic values such as openness, safety, and objective information are being ignored as Health Canada consciously opts instead for a drug regulatory system that reflects the interest of private industry.⁷⁷⁹

The present regulatory and operational reforms underway at Health Canada, including the *Blueprint for Renewal* and *Progressive Licensing*, stem from the move toward ‘smart regulation’. Underlying smart regulation is the concept of:

using the regulatory system to generate social and [health] benefits while enhancing the conditions for a competitive and involved economy that will attract investments and skilled workers and sustain a high quality of life for Canadians.⁷⁸⁰

This has meant that most new and existing regulatory activity has come to reflect an agenda promoting:

international competitiveness, risk management approaches, alternative instruments such as voluntary codes and regulatory compliance measures that ensure transparency and (business) stakeholder engagement.⁷⁸¹

This agenda has also become ingrained in guidance (the Cabinet Directive on

⁷⁷⁷P.C. Hebert, “Progressive Licensing needs Progressive Open Debate” (2007) 17(13) *CMAJ* 1801 801 at 801 (PUBMED).

⁷⁷⁸*Ibid.*

⁷⁷⁹*Going, supra* note 229.

⁷⁸⁰Government of Canada, Department of Finance, *A Plan for Growth and Prosperity: Executive Summary*, (Ottawa: Departments of Finance, 2005), online: <<http://www.fin.gc.ca/ec2005/agenda/agsum-eng.asp>>.

⁷⁸¹Government of Canada, Policy Research Initiative, *Foundation Paper: Instruments of Choice in Global Democracies* (Ottawa: Policy Research Institute, 2007), online: <<http://policyresearch.gc.ca>>.

Streamlining Regulation)⁷⁸² and a policy of reducing the overall regulatory intervention of government (see the Treasury Board's 'change agenda' and 'policy suite renewal').⁷⁸³

What this means for programs such as PLF is that they may, even unintentionally, be driven by a set of assumptions related to reduced regulatory intervention and increased autonomy of the regulated (in this case, the pharmaceutical industry). As Lemmens and Bouchard have noted, the question becomes "whose definition of health, safety, security and values are to guide the government in constructing and implementing its reform project?"⁷⁸⁴ If the project is not executed appropriately, the government "risks no longer being a protector of public health but a cheerleader for economic growth at the risk of public health".⁷⁸⁵ While PLF has many of the needed elements of an improved regulatory system, it also contains many elements that on closer examination could be considered as diminishing of the overall scrutiny and SEQ standards imposed on new drugs.

(b) The Downside to Progressive Licensing

One of the most cited criticisms and flaws in the PLF model and pharmacovigilance as a whole is the potential for shifting the regulatory oversight of new drugs from a pre-market review of SEQ to one based largely on post-market surveillance. Or as the editor of CMAJ has noted, "in exchange [for] the requirements to continuously

⁷⁸² CDSR, *supra* note 624.

⁷⁸³ See Government of Canada, Treasury Board of Canada Secretariat, 2009 *Report on Plans and Priorities* (Ottawa: Treasury Board of Canada Secretariat, 2009), online: <<http://www.tbs-sct.gc.ca/rpp/2009-2010/inst/tbd/tbd-eng.pdf>>.

⁷⁸⁴ Bouchard, *supra* note 440 at 65.

⁷⁸⁵ J. Graham, "Smart Regulation: Will the Government's Strategy Work" (2005) 173(12) *CMAJ* 1469 (PUBMED).

evaluate drugs post-market [the] threshold for approval of selected new drugs is lower”.

⁷⁸⁶ As Bouchard has noted:

The thrust of this critique is that the focus of PLF will be on industrial development rather than public protection, including a continued preference for access, faster review times, private IPR rights, and minimal post-marketing obligations.⁷⁸⁷

Health Canada has repeatedly asserted that this is not the intention of the PLF.⁷⁸⁸ Yet as has been noted in a recent empirical analysis of all approvals by TPD from 2001 to 2008, there has already been a slow shift at TPD towards “earlier access to drugs that occupy the ‘extraordinary need’ niche with emphasis on post-market surveillance”.⁷⁸⁹ There is already a trend toward relaxing the standards for ‘promising new therapies’ that places the burden for proving safety and efficacy of a new drug on a post-market consuming public.

There are two dangers in moving the demonstration of SEQ to post-market surveillance. The first is that ADRs (post-market safety events) are notoriously underreported and Health Canada has, as yet, to demonstrate that it can effectively receive, analyze, and disseminate adverse event information to patients and practitioners. Worldwide ADR reporting systems consistently only capture 1 to 10 per cent of all reactions⁷⁹⁰[and] that figure may be considerably lower”.⁷⁹¹ As one author has noted, much of PLF is pegged upon the quality of data that will be generated by

⁷⁸⁶P. C. Hebert, “Editorial: Progressive Licensing Needs Progressive Open Debate” (2007) 176(13) *CMAJ* at 1801 (PUBMED).

⁷⁸⁷*Bouchard, supra* note 440 at 64.

⁷⁸⁸See *PL Website, supra* note 352.

⁷⁸⁹See *Sawicka, supra* note 445. As can be expected from the US example, increasingly few of the post market studies are being fully met. See also *FDA Post Market, supra* note 740.

⁷⁹⁰L. Hazell & S. Shakir “Under Reporting of Adverse Drug Reactions: A Systematic Review” (2006) 29(5) *Drug Safety* 385 at 386 (HEINONLINE).

⁷⁹¹*Going, supra* note 229 at 12.

pharmacovigilance, which:

implies that this will not compromise safety, because a new and enhanced post market surveillance system will identify problems quickly and effectively. This is speculative and is not supported by evidence or by Health Canada's track record.⁷⁹²

At the time of drafting this thesis, Health Canada had as yet to produce a clear articulation of what a Canadian pharmacovigilance system would look like or encompass. Without a clear picture of how pharmacovigilance will manifest in Canada, it becomes difficult to gauge how effective its implementation would be. The PLF, which was already almost codified by Bill C-51, is dependent on this new post-market measurement.

No legislation should be passed without clearly identifying how pharmacovigilance will be dealt with and defining how it will be dealt with in regulations. There is a persistent danger that the good intentions of the legislative drafters and legislative review team will be lost if the parameters of pharmacovigilance and its effects on risk-benefit analysis are not spelled out well in advance. Based on the EU and U.S. models, pharmacovigilance (or at least pharmacovigilance planning) must supplement the traditional SEQ model, not become the deciding factor in a risk-benefit analysis.

The second is that repeatedly in the U.S. and Canada, industry has been shown to be slow – if not outright dilatory – to meet imposed conditions of post-market surveillance. Once a manufacturer has a product on the market, past patterns have suggested that there is little incentive to complete imposed conditions. A recent U.S.

⁷⁹²J. M. Wright, "Progressive Drug Licensing: An Opportunity to Achieve Transparency and Accountability" (2007) 176(3) *CMAJ* at 1848, online: <<http://www.cmaj.ca/cgi/reprint/176/13/1848>>.

congressional report on the meeting of post-market conditions imposed under the US-PDUFA has found that less than 10 per cent (out of over a thousand issued 2002-2005) have yet to be met.⁷⁹³ Similarly, in Canada a review of post-market conditions imposed on drugs issued an NOC has demonstrated that the vast majority of conditions associated with these products still remain unmet.⁷⁹⁴ Reviewing the 38 NOCs issued as of January 2008, Lexchin found little evidence that the majority of application sponsors had acted on the conditions imposed on licensing, including one NOC issued in August 2009 which had as yet to meet its imposed conditions. Any new model must impose obligations and severe consequences, including revocation of a drug's license, for failure to meet post-market commitments under very clearly defined timelines.

Another potential pitfall for PLF is how poorly it defines what will qualify as a drug for flexible departure. Presently, Health Canada has defined flexible departure as:

Deviation from the standard baseline requirement for evidence supporting a drug's efficacy and safety that is necessary for the drug to attain initial market authorization. There must be a compelling reason justifying such a departure from baseline standards.⁷⁹⁵

There is little clarity provided as to what would constitute a compelling reason, but PLF has defined 'extraordinary need' as "urgent medical need resulting from significant threat to human health, either individual or population-wide".⁷⁹⁶ In the U.S., the definition of a product that meets an urgent or unmet need has been interpreted by the courts and the FDA very broadly. This has meant that virtually all products can apply to be approved

⁷⁹³ *GOA Report, supra* note 706.

⁷⁹⁴ *Bouchard, supra* note 440 at 103.

⁷⁹⁵ *PLF website, supra* note 550 at Glossary.

⁷⁹⁶ *Ibid.*

using an expedited process;⁷⁹⁷ Vioxx was approved this way.⁷⁹⁸ In order to ensure that flexible departure does not become the norm for all new drugs, better parameters for when it could be used and the understanding that it should be used as an exception must be clearly integrated into the Progressive Licensing model.

A final difficulty for PLF is the degree to which it will be shifting the monitoring and assessment of SEQ to industry. Pharmacovigilance, regardless of the final form it takes, is a type of self-regulation whereby industry is given a larger role in defining its self-monitoring standards and overseeing the implementation of those standards. Instead of directly imposing or supervising SEQ, what Health Canada will actually oversee is that the regulated has a plan to oversee SEQ. As Lemmens has noted:

this represents a sea change in priority-setting in terms of shifting the focus of government from a conscious and active ‘gate keeping’ or fiduciary function in balancing public and private interest to a more tenuous, if not naive partnership with the private sector.⁷⁹⁹

There is a danger that “over time regulators tend to become advocates for the industry they are supposed to regulate, as a result of conflict avoidance and influence from industry”.⁸⁰⁰ Over time it is likely that industry will push for an expanded role for pharmacovigilance and an expanded role in self-monitoring. This drift towards increased self-regulation means that over time it will become more difficult for regulators to impose the conditions and standards that industry uses to self-monitor.

⁷⁹⁷GOA Report, *supra* note 706.

⁷⁹⁸Vioxx Lessons, *supra* note 20.

⁷⁹⁹Lemmens & Bouchard, *supra* note 774 at 356.

⁸⁰⁰J. Lexchin “Clinical Trails in Canada: Whose Interest are Paramount?” (2008) 38(3) *International Journal of Health Services* 525 at 538.

(c) General Statement

In the present chapter, I have tried to demonstrate that a policy shift has occurred in relation to pharmaceutical regulatory models. Proposed regulatory models are shifting away from a point in time approval of new drugs based on SEQ, to a model that assesses a drug's overall risk-benefit profile at the time of approval and continues to monitor the product's safety over its life-cycle. Stemming from the *Blueprint for Renewal*⁸⁰¹ and *Canadian Consumer Safety Action Plan*,⁸⁰² this policy has been embodied in the proposed Progressive Licensing model, which has a focus on ongoing safety monitoring, flexible departure for urgently needed new drugs, and pharmacovigilence. Much of the intent of this model was incorporated within the proposed Progressive Licensing model and Bill C-51⁸⁰³ that expanded regulator powers. Yet the form and implementation of these changes, including regulations and a clear new model for drug approvals, still remain largely to be determined and communicated by Health Canada.

Key to this new model of drug regulation are the ideas of risk-benefit analysis and pharmacovigilence. Yet as I have argued above, each of these regulatory tools is not without potential problems. Risk-benefit analysis must be applied judiciously and cannot be allowed to supplant existing SEQ standards or be based on benefits that have little to do with health. Pharmacovigilence also must ensure that it is not merely used as a mechanism to allow for the establishment of post-marketing surveillance plans in exchange for reducing pre-market SEQ data. To this effect, any new legislation must

⁸⁰¹*Blueprint, supra* note 559.

⁸⁰²*CDSR, supra* note 624

⁸⁰³*C-51, supra* note 544.

include clear language ensuring the supremacy of the SEQ standard being met as a dominant element in any risk-benefit analysis, and that pharmacovigilance be only an additional element required for drug approvals in addition to the demonstration of SEQ.

Designing a new drug regulatory regime is no easy process, as Lexchin has noted:

Absolute drug safety can never be achieved. The task of regulatory authorities such as Health Canada is to identify as many as possible of these problems before drugs are released onto the market; then to continue to monitor drugs' safer approval to ensure that any new safety issues are documented, and finally to be sure that this information is disseminated in an effective manner so that practitioners prescribe and patients use medicines in the safest and most beneficial way possible.⁸⁰⁴

The PLF model shows great promise for ensuring increased post-market surveillance of new drugs but it is also not without its potential pitfalls. Regulators must be cautious as they move forward in structuring a new drug regulatory model that consciously accounts for some of the dangers identified above, and focuses on health and safety rather than innovation and the pharmaceutical industry's needs.

⁸⁰⁴*Going, supra* note 229 at 14.

CHAPTER 6: CONCLUSION

The medieval philosopher Paracelsus once stated that “all medicines are poisonous... the right dose differentiates a poison from a remedy”.⁸⁰⁵ All medications contain the seed for great harm and great good. For the most part, we are better off for the existence of prescription pharmaceuticals. One author notes:

Tens of million of people are alive today who would be dead without their medicines, and tens of millions more have far less life-crushing disabilities because of prescriptions their doctors have written. Some others - though mercifully a much smaller number - become disabled or die when a drug’s risk-benefit balance goes horribly wrong.⁸⁰⁶

The benefits from pharmaceuticals are enormous, but this must be tempered with a realization that their uses must be justified through the provision of adequate and realistic data on SEQ.

As was noted earlier in this thesis, we place a lot of faith in science to give our decisions the weight of empiricism. Yet in those cases where science is used as a tool in regulatory decision-making, it must be employed correctly. If methodologies or sound scientific design are allowed to degrade as a result of low regulatory standards or poor policy, the research observations that flow from these studies become weak and their ability to demonstrate a drug’s safety or effectiveness become meaningless.

⁸⁰⁵ *Avorn, supra* note 34.

⁸⁰⁶ *Ibid.* at 17.

If those scientific standards degrade or are subject to misinformation, if the primary policy considerations of regulators cease to be related to the health of Canadians, and if those mechanisms in place guiding decisions lose their objectivity, then the ultimate loser is the health of the Canadian public. Scientific observation is not infallible or ethically neutral.

It took a development in humanist understanding to alter ancient medical models, which eventually led to a desire to research the value of new drugs. Science cannot operate on its own without guidance that sets limits on what it should be asking and how. Science does not provide us with the capacity for formulating ethical or moral decisions. Without some form of codified guidance for practices and priorities, science can become distorted, exploitative, and even destructive. It must be the product of deliberation and the establishment of values through human consideration. In regulatory decisions that have ethical implications, such as drug development and approval, establishing limits on how we use science must be the product of extended, accurate, and effectively consultative deliberation.

Vioxx Revisited

On November 9, 2007, Merck settled the U.S. Vioxx class action suit with nearly 27, 000 plaintiffs who had alleged damages and a pay-out of 4.85 billion dollars.⁸⁰⁷ The drug was pulled from the market in 2004, yet Merck had been aware of the dangers associated with the drug as far back as 2001. Throughout the litigation Merck pursued a

⁸⁰⁷*Vioxx Tactics*, *supra* note 143.

“try every case” philosophy and “backed its public litigation posture by paying millions of dollars in legal fees and other trial expenses, while running an extensive advertising campaign touting Merck’s contributions to public health”.⁸⁰⁸ This enabled Merck to settle for far less than was expected, and in fact to make a profit on its overall marketing of Vioxx.

Vioxx was a complete regulatory failure. The mechanisms in place to assess the safety and efficacy of this new drug failed to prevent the product from getting on the market, failed to ensure that the drug manufacturer was providing all relevant scientific evidence and conducting the appropriate research, and ultimately failed to ensure the product was monitored and removed from the market once the dangers were suspected. (Merck voluntarily removed the product.) The results of Vioxx’s failure rest to a large extent with the regulation failing to impose on drug manufacturers an obligation to relay all known dangers, and partially with the regulators for fast-tracking the drug’s release and not monitoring the effects of the drug once it was on the market.

Yet Vioxx represents only the most recent and infamous failure of the regulatory regime. As we have seen, all drug regulation can be seen as occurring on a pendulum which swings from access to safety. It is characterized by a severe public health event which is swiftly followed by increased regulatory oversight, new standards of safety, and with time, the slow movement away from broader health concerns, until the next event. This has occurred repeatedly; in the late 1800s with the adulteration of a simple lozenge that led to initial manufacturing standards, in the 1900s with the sulfimide disaster that

⁸⁰⁸*Ibid.* at 510.

led to initial safety standards and finally the thalidomide disaster in the 1960s that led to efficacy standards being ingrained in the modern clinical trial. From this we get the SEQ standard. The current push towards post-market surveillance (or pharmacovigilance) is arguably itself the product of the Vioxx debacle.

If Vioxx had been marketed under a different drug regulatory regime it is still conceivable that it would have been marketed without accounting for its long-term dangers. Under one potential reality, Merck would have merely been required to provide a risk management plan and proposal for long-term safety monitoring, which may or may not have been followed up (SEQ mitigated with PvP). Under another, it would have been required to provide a detailed long-term safety monitoring plan, met that plan, and that may have identified the dangers inherent in its long-term use (SEQ with added PvP). Regardless, present safety standards are inadequate to have imposed the needed rigour on the science used in the clinical trials and post market studies. As the present regulatory model develops it must ensure that it moves in a direction that holds improving the health of Canadians as its primary policy goal.

Hitting the Right Balance

Law and policy are critical in the formulation and administration of the drug regime.⁸⁰⁹ They provide certainty to applicants and guide those seeking drug approvals. Manufacturers will modify their behavior to meet the requirements of regulators. Where guidance is weak or allows for too much leeway, those employing the system are apt to

⁸⁰⁹*Ibid.*

exploit weaknesses. Applicants will seek to limit costs, reduce interaction with the regulatory body, and seek the most effective (timely and simple) way to ensure that their product is approved. The law establishing the approval process and the policies determining how it is enforced send a tacit message about a regulator's priorities and intentions. As noted earlier:

by defining the specific incentives, opportunities, and constraints within which private sector groups operate and assert their interests, institutions change the rules of politics and hence the context in which political power is determined.⁸¹⁰

We must be cognizant of the role that law and policy play in creating these realities for good or bad when assessing the validity of regulatory and legislative structures. For new drugs this means that science, policy, and law walk hand in hand in structuring the system that guides new drugs to the market.

Prescription drugs in Canada are big business. It is estimated that 25.4 billion dollars will be spent on prescription drugs over 2009-10 in Canada, with 11.4 billion of this being spent by privately-funded health-care programs.⁸¹¹ Drugs represent the second largest cost to the public health-care system after hospitals and Canadians pay more on average (per capita \$832 CAD) for prescription drugs than any other OECD country.⁸¹² In the past decade, expenditures have more than doubled, from \$12 billion to \$25 billion.⁸¹³ The regulation and oversight of this system affect all Canadians and the overall quality and functioning of our health-care system.

⁸¹⁰*Wiktorowicz, supra* note 24 at 618.

⁸¹¹See Canadian Institute for Health Information, *Drug Expenditures in Canada, 2002-2009* (Ottawa: CIHI, 2010), online: <<http://cihi.ca>>.

⁸¹²*Ibid.*

⁸¹³*Ibid.*

As the regulator, Health Canada plays an important role in overseeing and guiding the quality of the pharmaceuticals that are available in Canada. Yet as this thesis has demonstrated, there are significant gaps in the law overseeing the generation of scientific information. It is essential that in the review of new health products the regulator take into account as a primary policy consideration that these products be safe, efficacious, and of high quality. Only then should other considerations such as the product's market value, the potential for innovation, and the speed of drug review be considered.

Whither the Regulator

Each year all government departments are required to produce a report of their planned activities and performance on those activities called a Report on Plans and Priorities (RPP). The RPP serves to “describe departmental priorities, expected results and the associated resource requirements [to inform] parliamentarians and Canadians of departmental plans”.⁸¹⁴ Basically, the RPP serves as the outline for a department's plans, priorities, and intended activities over the coming next three years. In the 2002 RPP, Health Canada defined its role as “guardian/risk mitigator and information provider through the generation of shared knowledge”.⁸¹⁵ In Health Canada's 2009-10 RPP, it

⁸¹⁴Treasury Board of Canada, *Backgrounder – The 2009-10 Reports on Plans and Priorities* (Ottawa: Treasury Board of Canada Secretariat, 2009), online: < <http://www.tbs-sct.gc.ca/media/nr-cp/2009/0326-eng.asp>>.

⁸¹⁵Health Canada, *Health Canada: Report on Plans and Priorities (2002-03)* (Ottawa: Health Canada, 2002), online: < <http://www.tbs-sct.gc.ca/tbs-sct/cmn/archives-eng.asp> >.

identified its core responsibilities as “a regulator, service provider, funder”⁸¹⁶ and newly as a “catalyst for innovation and information provider”.⁸¹⁷

In the 2009-10 RPP, Health Canada has reaffirmed its intention to “update the regulatory system to address new realities in science and technology and the global economy”.⁸¹⁸ While there is no specific plan to re-introduce Bill C-51, Health Canada continues working on a new regulatory system largely based on the Canadian Consumer Safety Action Plan:

The Department will build on the initial thrust of the Action Plan and undertake a number of initiatives in each of the three pillars: *active prevention* to address as many potential problems as possible before they occur; *targeted oversight* so the government can keep a closer watch over products that pose a higher risk; and *rapid response* to enable government to take action more quickly and effectively.⁸¹⁹

These three new pillars for any drug regulatory system can rightly be observed as a shift to limited regulatory oversight pre-market against a priori identified risks in favour of responding when unforeseen risks occur.

This shift is core to how the government of Canada has begun to perceive its role as a provider of health services, from active participant to more of a third party facilitator of drug marketing. While it still regulates several product lines, it now conceives of this role as working to “generate and share knowledge and information on which personal

⁸¹⁶2010 RPP, supra 615.

⁸¹⁷*Ibid.*

⁸¹⁸*Ibid.*

⁸¹⁹*FCSAP*, supra note 561.

decision-making, regulations and standards, and innovation in health rely”.⁸²⁰ This reflects what was announced by TPD in its own *Business Transformation Strategy*, to:

speed up the regulatory process for drug approvals, to move forward with a smart regulation strategy to accelerate reforms in key areas to promote health and sustainability, to contribute to innovation and economic growth, and to reduce the administrative burden on business.⁸²¹

As Lexchin suggest, this new role is one where the regulator’s “main function is to facilitate industry’s efforts to develop new products and to approve them as quickly as possible... and the regulatory authority exists to provide a service to industry”.⁸²²

There is much promise in the model envisioned in Bill C-51 and Progressive Licensing, but there are also dangers. Under the life-cycle model greater monitoring and real-world information on drugs use would be generated, yet it remains unclear whether this will be at the expense of allowing products to be marketed with lower evidential (SEQ) standards, and based on a host of non-scientific policy risks or benefits. The question becomes, what will be the form of this new regulatory and legislative regime? As has been echoed throughout this thesis, when science is used it must be employed correctly. Creating a regime that in any way exchanges safety of the drug-consuming public for unproven measures of predictive safety based on risk modeling is fraught with peril.

⁸²⁰*Ibid.*

⁸²¹Health Canada, Therapeutic Products Directorate, *Therapeutic Products Directorate Business Transformation Report* (Ottawa: Health Canada, 2003), online: <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/bt_rep_to_rap_2003_04-eng.pdf>, accessed August 23, 2010.

⁸²²*Exce\$ive, supra* note 367.

Ultimately it is up to Health Canada and the government to decide how they will formulate this new regime. At its core government needs to compel better research and data provision by industry and strengthen the power of the regulator to enforce post-market research. Yet it must be cautious that in so doing it does not adopt a model that has greater policy and regulatory gaps. The new regime must be crafted to incorporate updated legal requirements for manufacturers and clinical researchers, but also fully articulate in law and regulation the new mechanisms (pharmacovigilance and risk-benefit analysis) that it proposed to adopt. If these mechanisms become an afterthought of the legislative and regulatory drafting, it is likely that they will not manifest as effective regulatory tools, and in the end lead to new drug failures.

We are left with the question: If Health Canada does not oversee the safety, efficacy and quality of these products, then who does? While imperfect, the present regime, and that envisioned by Progressive Licensing, represents an essential layer of protection for the drug consuming public. What is truly needed is a commitment from Health Canada and the Government to create a robust, adaptable, and evidence based drug regime that places the health and safety of Canadians above any other policy considerations.

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