THE MUD AND THE BLOOD AND THE BEER: CANADA'S PROGRESSIVE LICENSING FRAMEWORK FOR DRUG APPROVAL[1]

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Canada is currently undergoing a transition in its system of public health, including major redefinition of the duties, accountabilities and risks assumed by public and private actors responsible for developing, regulating, and consuming innovative therapeutic products. This has been accompanied by increasing political rhetoric to the effect that many distinct elements of Canada's health care system are functioning poorly or not at all, with great economic and quality of life costs for all Canadians. In particular, the nation's proposed new drug regime, termed the "Progressive Licensing Framework", has received considerable attention since the announcement of Bill C-51 in early 2008. Critics claim that expedited review, or so-called "flexible departure", may lead to a lower standard for drug approval and a further increase in unsafe products directed to the market. Supporters claim that more emphasis on post-market safety will effectively recalibrate the risks, benefits, costs, and uncertainties of therapeutic product development. Ironically, the focus of both groups is on the balancing function of drug regulation, as global governments seek to integrate the wide range of competing scientific, economic, and public health interests involved in innovative product development. This article reviews developments leading up to the focus on the "lifecycle" or "real world" approach to drug regulation, including shifts in the speed and mechanism of drug approval, the growth in intellectual property and regulatory rights attached to drug products, the effects of these developments on post-market safety, and the manner in which advocates of lifecycle regulation argue it will help solve certain post-market safety problems.

[1] The full lyric is "Kicking and a' gouging in the mud and the blood and the beer": from the song "*A Boy Named Sue*" sung by Johnny Cash, written by Shel Silverstein, and recorded on February 24, 1969 at San Quentin Prison (Columbia).

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ABBREVIATIONS[2]

ADR	Adverse Drug Reaction
ANDS	Abbreviated New Drug Submission
EMEA	European Medicines Ageny
FDA	Food & Drug Administration
GOC	Government of Canada
HPFB	Health Products & Food Branch
IOM	Institute of Medicine
IPR	Intellectual Property & Regulatory
NDS	New Drug Submission
NOC	Notice of Compliance
NOC/c	Notice of Compliance with conditions
PDUFA	Prescription Drug User Fee Act (US)
PLF	Progressive Licensing Framework
rTPL	regulated Therapeutic Product Lifecycle
TPD	Therapeutic Products Directorate
SNDS	Supplementary New Drug Submission
SANDS	Supplementary Abbreviated New Drug Submission
WHO	World Health Organization

INTRODUCTION

The Government of Canada (GOC) announced on February 8, 2008 that the *Food and Drugs Act*[3] and *Food and Drug Regulations*[4] would be substantially amended to make room for its new "Progressive Licensing Framework" (PLF) for drug approval. While the announcement occurred after at least two years of stakeholder consultations, it nevertheless set off a media storm, with voices from newsprint, internet, and radio outlets crying foul, including those of many experts in the field.[5] Stakeholders in the natural health product sector also opposed Bill C-51, alleging that up to three-quarters of natural health products would be unable to meet the requirements for approval under Bill C-51.[6] By contrast, supporters of PLF claim that an increased focus on post-market safety will effectively recalibrate the balance between access and safety and mitigate the ills of the last decade of

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[2] The following list comprises abbreviations that are used throughout this article.

[3] *Food and Drugs Act*, R.S.C. 1985, c. F-27.

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

[5] Carly Weeks, "New Drug Rules Pose Grave Risks: Critics" *The Globe and Mail* (8 February 2008) L6 (Jim Wright [UBC], Joel Lexchin [York], David Juurlink [Sunnybrook], Mary Wiktorowicz [York], Judy Wasylycia-Leis [NDP] and Michael McBane [Canadian Health Coalition] expressed concerns over the implications of PLF for patient safety); Carly Weeks, "Experts Sound Alarm on Drug-Approval Plan: Under Sweeping New Changes, Drug Companies Only Have to Prove That Benefit of Product Outweighs the Harm" *The Globe and Mail* (9 April 2008). See also "Manufacturers, Patient Groups Support Ottawa's New Drug Safety Proposals" *CBC News* (10 April 2008), online: CBC <http://www.cbc.ca/health/story/2008/04/09/drug-bill.html>; "Canada to Release Trial Drugs to Patients" *New Scientist* (21 April 2008) online: New Scientist <http://www.newscientist.com/channel/health/mg19826523.800-canada-to-release-trial-drugs-to-patients.html>; Carly Weeks, "Drug Recalls Linked to U.S. Testing Deadlines" *Globe and Mail* (27 March 2008).

[6] Spence Pentland, "Bill C51: Taking Away Your Right to Natural Health Products in Canada" *Acubalance Wellness Centre* (2 June 2008), online: Acubalance Wellness Centre <http://www.acubalance.ca/content/bill-c51-taking-away-your-right-natural-health-products-canada>; Shawn Buckley, "Bill C-51 Threatens Natural Health Products" *Health Action Network Society*, online: Health Action Network Society <http://hans.org/magazine/366/threatens-products-natural-health>; see also Martin Mittelstaedt, "Ottawa to Revive Supplement Safety Bill" *The Globe and Mail* (30 October 2008); Carly Weeks, "Critics Blast New Rules for Natural Remedies" *The Globe and Mail* (23 May 2008) (Some of the claims made include: "most of the herbal remedies for sale in Canada may soon be illegal" and "Canadian parents who give their children vitamins could face arrest". However, other commentators believe that Bill C-51 will not significantly affect the way natural health products are marketed and sold in Canada, but instead may bring accountability to the unregulated industry). In response to these concerns, GOC issued a statement clarifying that "Bill C-51 will not affect the way that natural health products are regulated in Canada, [that the] *Natural Health Product Regulations*, introduced in 2004, will continue to operate the same way under the proposed Bill [and that] Bill C-51 has been drafted to complement and support current policies for natural health products": Government of Canada, "Bill C-51 and Natural Health Products - The Facts", online: Healthy Canadians <http://www.healthycanadians.ca/pr-rp/billC-51_e.html>.

drug regulation. As alluded to in the title of this article, the architects of PLF clearly intend to roll up their sleeves to regulate what food and drug agencies in Canada,[7] the U.S.,[8] and the E.U.[9] have labelled "real world" drug safety and effectiveness. While a truism of sorts, the term is somewhat duplicitous. This is because it provides a certain degree of camouflage for the carefully orchestrated disconnect, vetted by major food and drug agencies, between the health status of clinical trial populations on whom drugs are tested and that of actual individuals consuming the products once they are approved. Nevertheless, it is safe to say that greater post-market oversight by GOC will be a welcome step for all parties to drug development, regulation, and consumption.

Progressive licensing is currently enshrined in Bill C-51,[10] which has had its second reading in Parliament to date. While its fate is uncertain at this moment in Canadian politics, provisions such as those encompassed by Bill C-51 are likely to come into force at some point in the near future. Parallel initiatives driven by a cascade of criticisms over existing linear models of drug approval have already been implemented in some form by other major drug agencies, including the U.S. Food and Drug Administration (FDA)[11] and the European Medicines Agency (EMEA).[12] Consistent with its 2006 National Pharmaceutical Strategy[13] and accompanying Smart Regulations strategy,[14] GOC sees itself as a leader both in developing an "innovative drug regulation" platform and providing "unique regulatory incentives" to the pharmaceutical industry.[15] In this capacity, drug regulators in Canada are no different from their American and European counterparts, all of whom claim that therapeutic prod-

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[7] Health Canada, "Real World Drug Safety and Effectiveness", online: Health Canada <http://www.hc-sc.gc.ca/hcs-sss/pharma/nps-snpp/securit/index-eng.php> [Health Canada, "Drug Safety"]. See particularly the description of the "distributed" and "centralized" new drug approval models: Health Canada, "4.0 Approaches to Strengthening the Evaluation of Real World Drug Safety and Effectiveness", online: Health Canada <http://www.hc-sc.gc.ca/hcs-sss/pharma/nps-snpp/securit/guide_4-eng.php>. See also Alan Cassels, "Institute of Medicine's New Drug Safety Report: Implications for Canada" (2006) 175 Canadian Medical Association Journal 1515.

[8] U.S., Institute of Medicine: Committee on the Assessment of the US Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Washington: National Academies Press, 2007), online: Institute of Medicine of the National Academies <http://www.iom.edu/CMS/3793/26341/37329.aspx> [*IOM Report*]. See also Gina Kolata, "The Evidence Gap—New Arena for Testing of Drugs: Real World" *New York Times* (25 November, 2008).

[9] European Medicines Agency: Evaluation of Medicines for Human Use, *Innovative Drug Development Approaches: Final Report from the EMEA/CHMP-think-tank Group on Innovative Drug Development* (London: European Medicines Agency, 2007) [*EMEA Innovation*].

[10] Bill C-51, *An Act to amend the Food and Drugs Act and to make consequential amendments to other Acts*, 2nd Sess., 39th Parl., 2008 [*Bill C-51*].

[11] U.S., Food and Drug Administration, "Fast Track, Accelerated Approval and Priority Review: Accelerating Availability of New Drugs for Patients with Serious Diseases" (May 2006), online: FDA <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm> [FDA Fast Track]. U.S., Food and Drug Administration: Department of Health and Human Services, "The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety" (May 2008), online: FDA <http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM124701.pdf> [FDA, "Sentinel"]. See also Gardiner Harris, "F.D.A. to Expand Scrutiny of Risks from Drugs after They're Approved for Sale" *The New York Times* (23 May 2008).

[12] EC, European Medicines Agency: Committee for Medicinal Products for Human Use (CHMP), *Guideline on the Scientific Application and the Practical Arrangements Necessary to Implement Commission Regulation (EC) No 507/2006 on the Conditional Marketing Authorisation for Medicinal Products for Human Use Falling Within the Scope of Regulation (EC) No 726/2004* (Doc. Ref. EMEA/509951/2006) (London: European Medicines Agency, 2006), online: EMEA <http://www.emea.europa.eu/pdfs/human/regaffair/50995106en.pdf> [*EMEA CHMP 1*]; EC, European Medicines Agency: Committee for Medicinal Products for Human Use (CHMP), *Report of the CHMP Working Group on Benefit-Risk Assessment Models and Methods* (London: European Medicines Agency, 2007), online: EMEA <http://www.emea.europa.eu/pdfs/human/brmethods/1540407en.pdf> [*EMEA CHMP 2*]; European Medicines Agency: Committee for Medicinal Products for Human Use (CHMP), *Reflection Paper on Benefit-Risk Assessment Methods in the Context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use* (Doc. Ref. EMEA/CHMP/15404/2007) (London: European Medicines Agency, 2008), online: EMEA <http://www.emea.europa.eu/pdfs/human/brmethods/1540407enfin.pdf> [*EMEA CHMP 3*].

[13] Federal/Provincial/Territorial Ministerial Task Force on the National Pharmaceuticals Strategy, *National Pharmaceuticals Strategy: Progress Report* (Ottawa: Health Canada, 2006), online: Health Canada <http://www.hc-sc.gc.ca/hcs-sss/alt_formats/hpb-dgps/pdf/pubs/2006-nps-snpp/2006-nps-snpp-eng.pdf> [*National Pharmaceuticals Strategy*].

[14] External Advisory Committee on Smart Regulation, *Smart Regulation: A Regulatory Strategy for Canada* (Ottawa: External Advisory Committee on Smart Regulation, 2004), online: Privy Council Office <http://www.pco-bcp.gc.ca/smartreg-regint/en/08/sum.html> [*Smart Regulations*].

[15] Robert Peterson, "Innovation in Drug Regulation: Canada as a Leader" (Lecture delivered at Ottawa Regional Conference: "Building Excellence in Clinical Research and Clinical Trials", 11 February 2005).

uct development is crucial for national prosperity and productivity in the global marketplace.[16] It is therefore not surprising that GOC sees its role not merely as a facilitator, but an "active participant" in driving the costs and risks of medical product development.[17]

The sections of Bill C-51 that have sparked the most debate are those granting GOC sweeping powers for clinical trial[18] and market[19] authorizations, including highly complex multi-stage evidentiary thresholds for suspension[20] and revocation[21] of clinical trial applications, market authorizations, and establishment licences. The Bill further gives GOC discretionary power to grant probationary approval for market authorization well ahead of approval typically granted after traditional Phase 3 clinical trials.[22] This process has been appropriately referred to by Health Canada in its policy and guidance documents as "flexible departure".[23] Another significant change from the existing approval regime is the express provision that the threshold for market authorization is where the "benefits outweigh the risks" of a new drug.[24] As such, the legal standard of evidence is ≥ 51% benefit-risk rather than a more substantial threshold of say 85%, 75%, or even 65%. Indeed, the preamble to Bill C-51 specifically states that Parliament recognizes that the "lack of full scientific certainty is not to be used as a reason for postponing measures that prevent adverse effects on human health."[25] This has led to predictions of the death, or at least the loss, of important limits imposed on regulatory decision making by reliance on the precautionary principle.[26] Concern has also been expressed over the reading-in of provisions incorporating strong intellectual property and regulatory (IPR) rights[27] and specific language contemplating incorporation into GOC policy and regulations, knowledge, documents, or information produced by industry and its trade organizations.[28] While it is reasonable to speculate that the latter provision is aimed at regulatory harmony and efficient incorporation into the drug approval exercise of technical information arising from global approval processes, there has been some unease that these practices are more in service of economic growth than GOC's public health mandate.[29] This reading is bolstered by statements from various branches of GOC itself.[30]

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16 Ron A. Bouchard, "Balancing Public and Private Interests in the Commercialization of Publicly Funded Medical Research: Is There a Role for Compulsory Government Royalty Fees?" (2007) 13 B.U.J. Sci. & Tech. L. 120 [Bouchard, "Balancing"].

17 Peterson, *supra* note 15 at 23.

18 *Bill C-51*, *supra* note 10 at cl. 8 ss. 18.2-18.6.

19 *Ibid.* at cl. 8 ss. 18.7-19.1.

20 For suspension with notice to sponsor, the threshold for clinical trial application and establishment licence is "preventing an injury" (cl. 8 ss. 15.5(1) and 19.6(1)) and for market authorization is "risks greater than benefit" (cl. 8 s. 19(1)) whereas for suspension without notice to sponsor, the threshold for clinical trial application, market authorization, and establishment licence is "serious and immanent risk of harm" (cl. 8 ss. 18.5(2), 19(2) and 19.6(2)).

21 For revocation with notice to sponsor, the threshold for clinical trial application, market authorization, and establishment licence is "breach of terms and condition" of authorization (cl. 8 ss. 18.6(1), 19.1(1), 19.7(1)) whereas for revocation with notice to sponsor, the threshold is "unacceptable risks" (cl. 8 s. 18.6(2)), "risks greater than benefit" (cl. 8 s. 19.1(2)) and "risk of injury to health" (cl. 8 s. 19.7(2)) for clinical trial application, market authorization, and establishment licence respectively.

22 Cl. 8 ss. 18.7-19.2, supported by powers granted cl. 8 s. 20.2, cl. 11 ss. 30(1)(s), (y), and (z.1), and 30.2(1).

23 Health Canada, "Blueprint for Renewal: Transforming Canada's Approach to Regulating Health Products and Food" (October 2006) at 14, 20, 38, 39, online: Health Canada <http://www.hc-sc.gc.ca/ahc-asc/alt_formats/hpfb-dgpsa/pdf/hpfb-dgpsa/blueprint-plan-eng.pdf> [Health Canada, "Blueprint"]; Health Canada, "The Progressive Licensing Framework Concept Paper for Discussion" at 20-24, online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/proglic_homprog_concept-eng.pdf> [Health Canada, "Concept Paper"]. See also Neil Yeates, David K. Lee & Maurica Maher, "Health Canada's Progressive Licensing Framework" (2007) 176 Canadian Medical Association Journal 1845 [Yeates].

24 *Bill C-51*, *supra* note 10 cl. 8 s. 18.7(1).

25 *Ibid.* at preamble, lines 20-23.

26 Mike McBane, "Health Canada Proposing to Eviscerate the Food & Drugs Act" 10:8 *The CCPA Monitor* 1 (February 2004); Janice Graham, "Smart Regulation: Will the Government's Strategy Work?" (2005) 173 Canadian Medical Association Journal 1469 [Graham, "Smart"]; B. Campbell & M. Lee, "Putting Canadians at Risk: How the Federal Government's Deregulation Agenda Threatens Health and Environmental Standards" *Canadian Centre for Policy Alternative Working Paper,* online: Canadian Centre for Policy Alternatives <http://www.policyalternatives.ca/documents/National_Office_Pubs/2006/Putting_Canadians_at_Risk_summary.pdf>.

27 *Bill C-51*, *supra* note 10 at cl. 11 s. 30(3).

28 *Ibid.* at cl. 11 s. 30(7)(b).

29 Graham, "Smart", *supra* note 26 at 1469.

This article traces the evolution of the lifecycle approach to drug regulation and provides an overview of its advantages and disadvantages based on contemporary legal and scientific norms. First, we describe the historical roots of the existing regime enshrined in the *Food and Drugs Act* and *Food and Drug Regulations*.[31] We then discuss several developments in drug regulation that combined have facilitated faster access to new drugs by the public. This includes the following: institution of a fee-for-service arrangement between food and drug agencies and sponsoring firms (user fees); other substantive and procedural mechanisms designed to speed access to new drugs in the presence or absence of market authorization; the evolution of the decision-making model underpinning drug approval away from the precautionary principle toward risk management principles; the accrual of domestic and global IPR rights explicitly designed to stimulate industrial pharmaceutical innovation; and the manner in which the IPR rights agenda has evolved over time to inform both limbs of the push-pull market dynamic for pharmaceutical products. We assess whether these changes, taken together, are associated with increased post-market drug safety problems such as drug withdrawals, black box warnings, and dosage form discontinuations.[32] We then describe the movement toward lifecycle, or real world models of drug regulation, including the shift toward PLF. Finally, we conclude with a review of concerns expressed over the global evolution toward the lifecycle approach, including those relating to PLF in Canada.

I
EVOLVING REGULATORY LANDSCAPE

A. Historical Framework

Under the *Constitution Act, 1867*,[33] GOC has jurisdiction over matters pertaining to the approval of pharmaceuticals. The Health Products and Foods Branch (HPFB), an entity of Health Canada, is responsible for granting market authorization for drugs.[34] HPFB's mandate is "to take an integrated approach to managing the health-related risks and benefits of health products and food by: minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health."[35] As such, the benefit-risk decision making and evidentiary framework for drug regulation and approval is embedded within HPFB's regulatory mandate.

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30 See *e.g.* the 2005 speech accompanying the launch of the government's Implementation Plan for Smart Regulation: Reg Alcock, "Government of Canada's Implementation Plan for Smart Regulations" (24 March 2005), online: Treasury Board of Canada Secretariat <http://www.tbs-sct.gc.ca/media/ps-dp/2005/0324_e.asp>; Health Canada, "Blueprint", *supra* note 23 at 8-9; Health Canada, "Concept Paper"*, supra* note 23 at 21; Peterson, *supra* note 15; Health Canada: Health Products and Food Branch, "Clinical Trials Regulatory Review—Stakeholder Workshop" (26 March 2007) at 6, online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ctrf_o_eccr_a_2007-03-26-eng.pdf> [Health Canada, "Stakeholder Workshop"]. See also Trudo Lemmens & Ron A. Bouchard, "Regulation of Pharmaceuticals in Canada" in Jocelyn Downie, Timothy Caulfield & Colleen Flood, eds., *Canadian Health Law and Policy*, 3d ed. (Toronto: LexisNexis, 2007) 311 [Lemmens & Bouchard].

31 *Food and Drugs Act*, *supra* note 3; *Food and Drug Regulations*, *supra* note 4.

32 A "black box warning" is a warning on the package insert for marketed drugs that the product may cause serious adverse reactions, or ADRs. The term arises from the black border that usually surrounds the text of the warnings. See U.S., Food and Drug Administration: Department of Health and Human Services, "Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format—Draft Guidance" (Rockville, MD: Center for Biologics Evaluation and Research, 2006) at 9, online: FDA <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf>.

33 *Constitution Act, 1867* (U.K.), 30 & 31 Vict., c. 3, s. 91 (27) reprinted in R.S.C. 1985, App. II, No. 5. The regulation of pharmaceuticals falls generally under the criminal head of power under s. 91(27) of the *Constitution Act, 1867*. Martha Jackman, "Constitutional Jurisdiction Over Health in Canada" (2000) 8 Health L.J. 95 at 96-99 (According to Jackman, the Supreme Court of Canada held in *R. v. Wetmore*, [1983] 2 S.C.R. 284 at 288, "that the provisions of the federal *Food and Drugs Act* relating to the safety of food, drugs and medical devices, were supportable under the criminal law power, inasmuch as they were directed at protecting the 'physical health and safety of the public'").

34 Lemmens & Bouchard, *supra* note 30 at 319.

35 Health Canada, "About Health Canada: Health Products and Food Branch", online: Health Canada <http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/index-eng.php>.

The Therapeutic Products Directorate (TPD) is responsible for granting market authorization for pharmaceutical drugs and medical devices intended for human use.[36] In order for authorization to be granted, a manufacturer must present "substantive scientific evidence"[37] of a product's "safety, efficacy and quality,"[38] as provided for under the provisions of the *Food and Drugs Act*[39] and *Food and Drug Regulations*.[40] As defined in the *Food and Drugs Act*,

> [a] 'drug' includes any substance or mixture of substances manufactured, sold or represented for use in (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals, (b) restoring, correcting or modifying organic functions in human beings or animals, or (c) disinfection in premises in which food is manufactured, prepared or kept.[41]

Substances regulated by Health Canada as drugs include prescription, non-prescription, brand name, and generic pharmaceuticals; vaccines; recombinant and blood related biologics; radiopharmaceuticals; homeopathic, traditional, and herbal natural health products; disinfectants; and veterinary medications.[42]

The process for drug approval in Canada has been divided historically into four phases: (1) pre-clinical studies; (2) clinical trials; (3) drug submission; and (4) approval and marketing. Pre-clinical studies are basic scientific studies that verify the safety of potential drugs, their potential therapeutic uses and the existence and extent of their toxic effects in animals.[43] They include all *in vitro*, *in vivo* and animal model experiments.[44] Based on the results of pre-clinical studies, a drug manufacturer or sponsor may apply, by virtue of a clinical trial application[45] to the TPD for approval to conduct clinical trials on humans.[46] Health Canada reviews the applications and notifies the sponsor within 30 calendar days if the application is found to be deficient; if the application is deemed acceptable, a No Objection Letter is issued within the 30-day review period.[47] A clinical trial application "contains information and documentation to support the objectives and goals of the proposed clinical trial" and "data that supports the drug product quality."[48] "The clinical and quality components of the application are reviewed in parallel and both must be satisfactory before a No Objection Letter can be issued."[49] The approval of local/institutional Research Ethics Boards at each institution must also be obtained before a clinical trial is initiated.[50]

The existing legislation and regulations contemplate distinct categories of clinical trials,[51] which will almost certainly change when PLF comes into force. These are Phases 1-4.[52] Phase 1 trials are the first studies in which a new drug is tested in humans.[53] They are conducted on small populations

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36 Health Canada, "About Health Canada: Therapeutic Products Directorate", online: Health Canada <http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/tpd-dpt/index-eng.php>.

37 Lemmens & Bouchard, *supra* note 30 at 326-28.

38 Health Canada, "Drugs and Health Products: Drug Products", online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index-eng.php>.

39 *Food and Drugs Act*, *supra* note 3 at s. 30.

40 *Food and Drug Regulations*, *supra* note 4 at s. C.08.002(2)(h).

41 *Food and Drugs Act*, *supra* note 3 at s. 2.

42 *Ibid.*

43 Lemmens & Bouchard, *supra* note 30 at 321.

44 *Ibid.*

45 Health Canada, "Guidance for Clinical Trial Sponsors: Clinical Trial Applications", online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec_e.html#3> [Health Canada, "Clinical Trial Applications"].

46 Lemmens & Bouchard, *supra* note 30 at 321; *Food and Drug Regulations*, *supra* note 4 at s. C.05.004.

47 Health Canada, "Food and Drugs Act and Regulations: Background", online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_background-eng.php> [Health Canada, "FDAR Background"]. See also *Food and Drug Regulations*, *supra* note 4 at s. C.05.006.

48 Health Canada, "FDAR Background", *ibid.* See also *Food and Drug Regulations*, *supra* note 4 at s. C.05.005.

49 Health Canada, "FDAR Background", *ibid.*

50 *Ibid.*; *Food and Drug Regulations*, *supra* note 4 at s. C.05.006(1)(c).

51 *Food and Drugs Act*, *supra* note 3; *Food and Drug Regulations*, *supra* note 4 at s. C.05.004. For a definition of "clinical trial" see *Food and Drug Regulations, supra* note 4 at s. C.05.001.

52 Lemmens & Bouchard, *supra* note 30 at 321-25 and references therein.

53 *Ibid.* See also Health Canada, "Clinical Trial Applications", *supra* note 45; *Regulations Amending the Food and Drug Act Regulations* (*1024 - Clinical Trials*), S.O.R./2001-203; Health Canada: Health Products and Food Branch, *Guidance for Industry: General Considerations for Clinical Trials, ICH Topic E8*, (Ottawa: Public Works and Government Services Can-

(20-80) of healthy volunteers and aim to explore the general pharmacological and pharmacokinetic properties of the drug in question. Phase 2 trials involve larger (100-300) populations of patients who suffer from the disease for which the drug has been developed. The goal of these studies is to evaluate the efficacy of the drug and its short-term side effects. Phase 3 trials typically involve randomized double-blind controlled trials on about 1000-5000 patients, the focus being to determine not only efficacy but also long-term effects, including side effects. Whereas Phase 1-3 trials are currently conducted prior to a drug's market authorization, Phase 4 trials are performed once a drug has been approved. Historically, Phase 4 trials have been aimed at assessing long-term efficacy, different routes of administration, and whether the drug in question differs significantly from other drugs of the same class already on market.[54] However, as discussed in detail below, the nature of Phase 3-4 trials and the nature of scientific evidence required for approval is almost certain to change once PLF is fully integrated into the nation's regulatory regime.

Where Phase 1-3 trials demonstrate that the potential therapeutic benefits of a given new pharmaceutical outweigh its potential risks, the drug manufacturer may file a New Drug Submission (NDS).[55] The NDS contains data on drug safety, efficacy, and quality, including data from all relevant preclinical studies and clinical trials pertaining to a drug's manufacturing, packaging, labelling, claimed therapeutic value, conditions for use, and side effects.[56] A Supplemental New Drug Submission (SNDS) may be filed by a manufacturer for changes to a drug product already marketed by that sponsor.[57] These changes often include amendments to dosage, strength, formulation, method of manufacture, labelling, route of administration, or even indication.[58] Products associated with an SNDS are typically referred to as "line-extensions" (Line Extensions) of an already marketed drug. By contrast, a "me too" (Me Too) drug is typically not the first product on market for a given indication and chemical class. While a typical Me Too drug does not necessarily offer a better benefit-risk profile than previously approved comparator(s) for that indication, it does offer a better therapeutic option.[59] By contrast, a "first in class" (First in Class) drug has no comparator at all. First in Class drugs can be either new (NDS) or supplementary (SNDS) submissions.[60]

Manufacturers of generic drugs submit an Abbreviated New Drug Submission (ANDS) in order to obtain market authorization. An ANDS requires that the generic drug (e.g., sildenafil, vardenafil, and tadalafil) be pharmaceutically equivalent to the reference brand name product (e.g., Viagra, Levitra, and Cialis).[61] In this context, "equivalence" means that the generic product must be the same as the reference product with regard to (a) chemistry, (b) manufacturing, (c) route of administration, (d) conditions of use, and (e) therapeutic and adverse systemic effects when given to patients under the same conditions.[62] Similar to brand name sponsors, generic sponsors may also submit Supple-

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ada, 1997), online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e8-eng.pdf>. See generally Health Canada: Health Products and Food Branch, "ICH Guidance E6: Guideline for Good Clinical Practice: Consolidated Guideline" (1997), online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6_e.html>.

54 Lemmens & Bouchard, *supra* note 30 at 321-25.

55 *Ibid.* at 325; *Food and Drug Regulations*, *supra* note 4 at s. C.08.002(1)(a).

56 Lemmens & Bouchard, *supra* note 30 at 325; *Food and Drug Regulations*, *supra* note 4 at s. C.08.002(2). For details, see Health Canada: Health Protection Branch, "Preparation of Human New Drug Submissions: Therapeutic Products Programme Guideline" (1991), online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/prephum-eng.pdf>.

57 *Food and Drug Regulations*, *supra* note 4 at s. C.08.003.

58 Lemmens & Bouchard, *supra* note 30 at 326; *Food and Drug Regulations*, *supra* note 4 at s. C.08.003(2).

59 Personal communications with David K. Lee (Director, Office of Legislative and Regulatory Modernization, Policy Planning and International Affairs Directorate [PPAID], HPFB, Health Canada), Dr. Maurica Maher (Senior Scientific Advisor, Progressive Licensing Project, TPD, Health Canada) and Ms. Lesley Brumell (Supervisor, Submissions Processing, Submission and Information Policy Division [SIPD], Health Canada) during the period April-July 2008 [Health Canada Personal Communication].

60 The definitions of "First in Class", "Line Extension", and "Me Too" drugs employed by Health Canada are further developed in the companion article: Monika Sawicka & Ron A. Bouchard, "Empirical Analysis of Canadian Drug Approval Data 2001-2008: 'Doing More With Less'" 3 McGill J.L. & Health.

61 Lemmens & Bouchard, *supra* note 30 at 326. For definition of "Canadian reference product" and "pharmaceutical equivalent", see *Food and Drug Regulations*, *supra* note 4 at s. C.08.001.1.

62 Lemmens & Bouchard, *supra* note 30 at 326; *Food and Drug Regulations*, *supra* note 4 at C.08.002.1(1).

mental Abbreviated New Drug Submissions (SANDS) where certain changes are made to a generic drug that is already on the market. Consequently both brand name and generic firms can make "new" and "supplemental" submissions.

The HPFB subsequently reviews NDS, SNDS, ANDS and SANDS to assess the safety, efficacy, and quality of the drug candidates, as well as potential risks and benefits of the product.[63] Different classes of therapeutic products have different target times for screening and completion of reviews. For instance, the screening and review times for standard submissions by brand name firms of NDS and SNDS are 45 and 300 days respectively.[64] Conversely, with respect to generic submissions of ANDS and SANDS, the screening and review times are 45 and 180 days.[65] Once all regulatory requirements pertaining to safety, effectiveness, and quality have been met, and where the therapeutic benefits of a new drug outweigh its risks and those risks can be managed, a drug manufacturer is issued a Notice of Compliance (NOC).[66] In the case of generic drugs (ANDS and SANDS), an NOC is issued where the generic drug in question is deemed to be bioequivalent to the Canadian reference product. If a given pharmaceutical does not comply with all the necessary requirements, a Notice of Non-Compliance is issued with opportunity for appeal.[67]

B. Speed of Approval

One of the most important goals of drug regulation writ large over the last two decades is the issue of "access". One might properly ask: access to what? The question is a vital one as different actors in a complex[68] regulated Therapeutic Product Lifecycle (rTPL) innovation ecology[69] will answer it differently, with varying levels of fiduciary obligation.[70] Even so, the public, or at least certain segments of it, have demanded rapid access to "novel therapeutic products," and they have largely gotten their way. In Canada and the U.S., considerable resources have been spent to ensure faster drug approval.[71] Primary among these, the *Prescription Drug User Fee Act*[72] (PDUFA) was enacted by U.S. Congress in 1992. PDUFA authorizes the collection of user fees by the FDA from producers of new research-based drugs and biotechnology products.[73] Some commentators have suggested that user fees result in a significant reduction in the standard for review and a concomitant increase in

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63 Lemmens & Bouchard, *supra* note 30 at 326.

64 Health Canada: Health Products and Food Branch, *Access to Therapeutic Products: The Regulatory Process in Canada* (Ottawa: Health Canada, 2006) at 11, online: Health Canada <http://www.hc-sc.gc.ca/ahc-asc/alt_formats/hpfb-dgpsa/pdf/pubs/access-therapeutic_acces-therapeutique-eng.pdf> [*Health Canada Access to TP*].

65 *Ibid.*

66 *Food and Drug Regulations*, *supra* note 4 at s. C.08.004(1)(a). See also Health Canada, "Notice of Compliance" *Drugs and Health Products*, online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/index_e.html>.

67 *Food and Drug Regulations*, *supra* note 4 at s. C.08.004(1)(b).

68 John H. Miller & Scott E. Page, *Complex Adaptive Systems: An Introduction to Computational Models of Social Life* (Princeton, NJ: Princeton University Press, 2007) at 9 ("In a complicated world, the various elements that make up the system maintain a degree of independence from one another. Thus, removing one such element [which reduces the level of complication] does not fundamentally alter the system's behavior apart from that which directly resulted from the piece that was removed. Complexity arises when the dependencies among the elements become important. In such a system, removing one such element destroys system behavior to an extent that goes well beyond what is embodied by the particular element that is removed. Complexity is a deep property of a system, whereas complication is not.")

69 William Wulf, "Changes in Innovation Ecology" (2007) 316 Science 1253; Ron A. Bouchard, "KSR v. Teleflex Part 2: Impact of U.S. Supreme Court Patent Law on Canadian and Global Systems-Based Innovation Ecologies" (2007) 15 Health L.J. 247 [Bouchard, "Systems"]; Ron A. Bouchard, "Reflections on the Value of Systems Models for Regulation of Medical Research and Product Development" (2008) 17 Health L. Rev. 28 [Bouchard, "Reflections"].

70 Bouchard, "Balancing" *supra* note 16; Ron A. Bouchard, "Living Separate and Apart is Never Easy: Inventive Capacity of the PHOSITA as the Tie that Binds Obviousness and Inventiveness" (2007) 4 University of Ottawa Law & Technology Journal 1 [*Bouchard, "*Living"].

71 Lemmens & Bouchard, *supra* note 30 at 337.

72 *Prescription Drug User Fee Act*, 21 U.S.C. § 343-379g (2006) [*PDUFA*]. See generally U.S., Food and Drug Administration, "Prescription Drug User Fees", online: FDA <http://www.fda.gov/oc/pdufa/>.

73 David J. Cantor, "Prescription Drug User Fee Act of 1992: Effects on Bringing New Drugs to Market" *CRS Report for Congress* (12 September 1997), online: Policy Archive <https://www.policyarchive.org/bitstream/handle/10207/459/97-838_19970912.pdf?sequence=1>.

risk for the drug-consuming public.[74] Others have vigorously denied this,[75] claiming that PDUFA has provided necessary resources to expand review staff so that drug reviews can be completed within a certain time frame in the absence of revision to the standard for drug approval.[76]

The purpose of levying user fees was to enable the FDA to mitigate the regulatory burden on itself and pharmaceutical firms by augmenting staff and resources in order to accelerate review and enhance access.[77] Importantly, the FDA is not formally obligated to approve drugs faster in exchange for fees.[78] Rather, the onus is on the FDA to "review and act on" drug and biological submissions, with a focus on issuance of an action letter after review of the submission file. A 2002 U.S. General Accounting Office (GAO) report found that PDUFA funds allowed the FDA to increase the number of new drug reviewers by 77% in the first eight years of PDUFA, with a drop in median approval time for non-priority new drugs from 27 months to 14 months over the same period.[79] Using an elegant statistical analysis, Berndt *et al.* found that mean approval times for new molecular entities declined continuously following the coming into force of PDUFA I (1992), II (1997) and III (2002), from 33.6 months in a 1979-1986 year bin to 28.2, 18.6, and 16.1 months in the subsequent 1986-1992, 1992-1997, and 1997-2002 bins.[80] Comparing data trends pre- and post-PDUFA, the authors estimated that approval times would have declined even in the absence of user fees by about 1.7% annually, from 30 months in 1979 to 20 months in 2002. However, the data also demonstrated that the slope of the actual decline in review times was much steeper (25%) following the coming into force of PDUFA I and II. Similarly, Rawson and Kaitin reported that the median approval time for new drugs decreased from 713 days in 1992 with a load of 62 applications to 393 days in 2001 with a load of 25 applications.[81] User fees are also collected by the EMEA,[82] with the goal of industry fees eventually accounting for 75% of agency funding.[83]

User fees were introduced informally in Canada as early as 1995 in order to recover the bureaucratic costs associated with drug approvals and create incentives for regulators to speed up the regulatory process.[84] As in the U.S., industry requested a faster drug approval process in return for fees.[85] By 1997, approval times had decreased substantially: the median approval time was 490 days with a load of 39 applications compared with 405 days with a load of 43 applications in the U.S.[86] By 1999, it was estimated that user fees accounted for ~70% of the cost of running the TPD.[87] The Canadian

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74 Mary E. Wiktorowicz, "Emergent Patterns in the Regulation of Pharmaceuticals: Institutions and Interests in the United States, Canada, Britain and France" (2003) 28 J. of Health Politics 615; Laura Eggertson, "Drug Approval System Questioned in US and Canada" (2005) 172 Canadian Medical Association Journal 317; Joel Lexchin, "Drug Withdrawals from the Canadian Market for Safety Reasons, 1963–2004" (2005) 172 Canadian Medical Association Journal 765 [Lexchin, "Withdrawals"]; R. Horton, "The FDA and Lotronex: A Fatal Erosion of Integrity" (2001) 357 Lancet 1544.

75 John Graham, "Approving New Medicines in Canada: Health Canada Needs a Dose of Competition" (June 2005) Fraser Forum 9 [Graham, "Dose"].

76 Steven K. Galson, "The FDA and the IOM Report", Letter to the Editor (2007) 357 New Eng. J. Med. 2520.

77 Cantor, *supra* note 73 at 1.

78 Ernst R. Berndt *et al.*, "Industry Funding of the FDA: Effects of FDUFA on Approval Times and Withdrawal Rates" (2005) 4 Nature Reviews Drug Discovery 545 at 545 [Berndt *et al.*]; Daniel Carpenter, Evan James Zucker & Jerry Avorn, "Drug-Review Deadlines and Safety Problems" (2008) 358 New Eng. J. Med. 1354 at 1355 [Carpenter *et al.*].

79 U.S., General Accounting Office, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals and Other Agency Activities—Report to the Chairman, Committee on Health, Education, Labor, and Pensions, U.S. Senate* (S. Doc. No. 02-958) (Washington, D.C.: United States Government Printing Office, 2002) at 3, 8, online: GAO <http://www.gao.gov/new.items/d02958.pdf> [*USGAO User Fees*].

80 Berndt *et al.*, *supra* note 78 at 546.

81 Nigel Rawson & Kenneth Kaitin, "Canadian and US Drug Approval Times and Safety" (2003) 37 The Annals of Pharmacotherapy 1403 at 1404 (note, these figures are from an "industry-sponsored study" [Rx&D]).

82 Ines M. Vilas-Boas & C. Patrick Tharp, "The Drug Approval Process in the U.S., Europe, and Japan: Some Marketing and Cost Implications" (1997) 3 Journal of Managed Care Pharmacy 459. See also EU, European Medicines Agency, *Road Map to 2010: Preparing the Ground for the Future (Doc. Ref: EMEA/H/34163/03/Final)* (4 March 2005), online: EMEA <http://www.emea.europa.eu/pdfs/general/direct/directory/3416303enF.pdf> [*EMEA Road Map*].

83 Berndt *et al., supra* note 78 at 546.

84 Graham, "Dose", *supra* note 75 at 9.

85 J. Lexchin, "Transparency in Drug Regulation: Mirage or Oasis" at 9, online: Canadian Centre for Policy Alternatives <http://policyalternatives.ca/index.cfm?act=news&do=Article&call=913&pA=94761C2A&type=5>.

86 Rawson & Kaitin, *supra* note 81 at 1404.

87 Lexchin, "Withdrawals", *supra* note 74 at 765, citing: KPMG Consulting, "Review of Therapeutic Products Pro-

User Fees Act[88] came into force in 2004, in part due to continued complaints over the relatively slow approval process in Canada.[89] About the time the *User Fees Act* was passed, the average approval time in Canada had increased from a low of 490 days in 1997[90] to about 621 and 820 days in 2003 and 2004, respectively.[91] Since then, approval times have dropped again. Review times for 2007 reported by GOC were 247, 499, and 467 days for priority, standard, and total new drug submissions and 219, 344, and 341 days for priority, standard, and total abbreviated submissions.[92] The data reviewed thus far illustrate that user fees legislation has been successful where implemented in reducing approval times for drugs. The increase in speed of review applies to drugs and biologics entering both standard and expedited review streams. The study by Brandt *et al.* provides evidence to suggest that the decline in approval times triggered by user fee legislation is significantly steeper than the reduction in review times that may have been ongoing prior to PDUFA.[93]

Apart from user fees, a number of other factors have combined to increase approval speed and enhance access to new drugs.[94] This includes a number of administrative and technological developments designed to streamline the review process, higher quality applications, efforts toward global regulatory harmony, enhanced focus on leveraging knowledge gained from reviews in other jurisdictions, advocacy by real and apparent patient advocacy groups, and cultural changes within agencies themselves resulting from increasing partnership between industry and regulators.[95] Perhaps the most important of these however are policies and programs aimed at making drugs available to the public in a more expedient fashion.[96] As early as 1996, Health Canada issued a policy statement entitled *Priority Review of Drug Submissions* (Priority Review).[97] This policy provided for the "fast-tracking" of eligible NDS and SNDS intended for the treatment, prevention, or diagnosis of serious, life-threatening, or severely debilitating diseases or conditions for which there existed an unmet medical need or for which a substantial improvement in the benefit-risk profile of the therapy was demonstrated.[98] Drugs intended for conditions such as HIV/AIDS, Alzheimer's, Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease), angina pectoris, heart failure, and cancer, among others, were targeted for Priority Review.[99] Importantly, the same safety, efficacy, and quality criteria were required for the Priority Review process as for standard drug submissions—the main difference being the accelerated review time.[100] Target times for screening and review of Priority Review submis-

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gramme Cost Recovery Initiative" (Ottawa: Ministry of Health, 2000). Joel Lexchin has recently suggested that 50% of the budget for drug review now comes from user fees (Joel Lexchin, personal communication [22 October 2006], cited in Lemmens & Bouchard, *supra* note 30 at 318), a figure which tracks that in the US of about 53% in 2004, up from 7% in 1993: Anna W. Matthews, "Drug Firms Use Financial Clout to Push Industry Agenda at FDA" *The Wall Street Journal* (1 September 2006) A1.

88 S.C. 2004, c. 6.

89 Nigel S.B. Rawson, "Time Required for Approval of New Drugs in Canada, Australia, Sweden, the United Kingdom and the United States in 1996-1998" (2000) 162 Canadian Medical Association Journal 501; see generally Graham, "Dose", *supra* note 75 at 9.

90 Rawson & Kaitin, *supra* note 81 at 1404.

91 Joel Lexchin, "Drug Approval Times and User Fees: An International Perspective in a Changing World" (2008) 22 Pharmaceutical Medicine 1 at 8.

92 Health Canada: Health Products and Food Branch, *Annual Drug Submission Performance Report: Part I* (Therapeutic Products Directorate, 2007), online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/docs/perform-rendement/ar-ra/tpd_dpt_annual_annuel_07-eng.php> at 11, 34. As of April 14th 2009, Health Canada has not yet released its 2008 Annual Report.

93 Berndt *et al.*, *supra* note 78.

94 See Letter to the Editor from FDA Officials and subsequent Correction by the authors: Clark Nardinelli, Michael Lanthier & Robert Temple, "Drug Review Deadlines and Safety Problems" (2008) 359 New Eng. J. Med. 95; Daniel Carpenter, "Reply to Letter to the Editor" (2008) 359 New Eng. J. Med. 96 [Carpenter, "Reply"]. See also Berndt *et al.*, *supra* note 78; Hans-Georg Eichler *et al.*, "Balancing Early Market Access to New Drugs with the Need for Benefit/Risk Data: A Mounting Dilemma" (2008) 7 Nature Reviews Drug Discovery 818.

95 Bouchard, "Balancing", *supra* note 16; Bouchard & Lemmens, *supra* note 30.

96 For review, see Eichler *et al.*, *supra* note 94.

97 Health Canada, "Guidance for Industry: Priority Review of Drug Submissions" (2008), online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/priordr-eng.pdf> [Health Canada, "Priority Review"].

98 *Ibid.* at 1-2.

99 *Ibid.*

100 Lemmens & Bouchard, *supra* note 30 at 328; Health Canada, "Priority Review", *supra* note 97.

sions have now been shortened to 25 and 180 calendar days, respectively, from 45 and 300 days for non-priority submissions.[101] In short, Priority Review ensures that drug manufacturers jump ahead of others in the approval queue.[102]

In addition to Priority Review, a drug manufacturer or sponsor may be granted an NOC with conditions (NOC/*c*) if certain imposed requirements are satisfied.[103] According to Health Canada, "the NOC/c Policy applies to a New Drug Submission (NDS) or Supplemental New Drug Submission (SNDS) for a serious, life-threatening, or severely debilitating disease or condition for which there is promising evidence of clinical effectiveness based on the available data that the drug has the potential to provide: 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 such that the overall benefit/risk profile is improved over existing therapies, preventatives, or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada."[104] An NOC/*c* is essentially granted to expedite patient access to potentially life-saving drugs under circumstances of dire illness.[105] In addition to less onerous evidentiary requirements, the review process itself is also significantly accelerated, as targeted screening and review times for an NOC/*c* are 25 and 200 calendar days respectively.[106] The NOC/*c* policy grants a drug manufacturer or sponsor market authorization for the pharmaceutical in question on the condition that it performs additional studies to confirm the drug's alleged therapeutic benefit. The HPFB has, by virtue of the *Food & Drugs Act* and regulations, nominal jurisdiction to ensure a manufacturer's compliance through post-market surveillance.[107]

It has been claimed that the lack of specific legislative provisions allowing for contextual pre-market and post-market decision making relating to approvals under the NOC/*c* and Priority Review streams is one of the main drivers for reform of the nation's drug approval regime.[108] NOCs granted in accordance with NOC/*c* and Priority Review policies are currently issued under the general licensing provisions of the *Food and Drug Regulations*,[109] rather than provisions specific to either expedited review pathway. Licences are granted under the terms of C.08.004(1), modified by evidentiary requirements specific to the "conditions for use" provided for under C.08.002(1), particularly C.08.002(1)(g), and C.08.002(1)(h). Parallel provisions exist with regard to drugs used in the context of clinical trials under C.05.006(2)(a). These provisions are enabled by s. 30(o)(ii) of the *Food and Drugs Act*, which provides GOC with the jurisdiction to make regulations respecting the "sale or conditions of sale of any new drug".[110] If evidence or new information arises after issuance of an NOC/*c*, or an NOC under the Priority Review stream, to the effect that the "conditions of use" are contravened, the Minister of Health may suspend an NOC/*c* or NOC under the provisions of C.08.006(1) and C.08.006(2). What contextual standards and mechanisms do exist for both review mechanisms are those based on policies contained in Health Canada "guidance documents".[111] Guid-

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[101] *Health Canada Access to TP*, *supra* note 64 at 11. See also Health Canada, "Priority Review of Drug Submissions", online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/prfs_tpfd-eng.php> ("Health Canada believes it is in the best interests of Canadians to review potentially life-saving drugs as early as possible." Therefore, "Priority Review submissions are inserted into Health Canada's drug submission queue in accordance with a shortened review target and, as such, may be reviewed in advance of non-priority submissions.")

[102] Health Canada Personal Communication, *supra* note 59.

[103] NOC/*c* is granted pursuant to s. C.08.004(1), in compliance with the conditions of use stipulated in s. C.08.002(1)(g), C.08.002(1)(h), C.08.006(2)(b), C.05.006(2)(a).

[104] Health Canada, *Guidance for Industry: Notice of Compliance with conditions (NOC/c)* (2006), online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/noccg_accd-eng.pdf> [*NOC/c Guidance Document*].

[105] Lemmens & Bouchard, *supra* note 30 at 329.

[106] *Health Canada Access to TP*, *supra* note 64.

[107] Lemmens & Bouchard, *supra* note 30 at 329. See also Health Canada, "Blueprint", Health Canada, "Concept Paper", and Yeates, supra note 23.

[108] Health Canada, "Blueprint", and Health Canada, "Concept Paper", *supra* note 23; Peterson, *supra* note 15.

[109] *Food and Drug Regulations*, *supra* note 4. See also Health Canada, "Notice of Compliance with conditions (NOC/*c*)" *Drugs and Health Products*, online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php>.

[110] *Food and Drugs Act*, *supra* note 3 at s. 30(o)(ii).

[111] Health Canada, "Priority Review", *supra* note 97; *NOC/c Guidance Document*, *supra* note 104.

ance documents are "administrative instruments" that are "meant to provide assistance to industry and health care professionals on how to comply with the policies and governing statutes and regulations."[112] While they have no force of law, GOC nevertheless claims that inclusion of the regulatory mechanisms therein allows for enhanced regulatory flexibility under certain conditions.[113]

In addition to Priority Review and NOC/*c*, Health Canada also allows physicians to gain access through its Special Access Programme to non-marketed drugs and medical devices that have not yet been approved for sale in Canada, provided that a patient has a serious or life threatening condition and where conventional therapies have failed, are unavailable, or are unsuitable.[114]

C. Mechanism of Approval

Along with the time for approval, there have also been significant shifts in the mechanism of drug approval over the last decade that have potentially accelerated the approval process and promoted access. The established decision-making framework for drug approval, as provided for in the *Food and Drugs Act* and *Food and Drug Regulations*,[115] is referred to as the "precautionary principle". The term is often used in reference to Galen's injunction to "first, do no harm" (*primum non nocere*). This means that, when an activity raises a significant threat of harm to human health, precautionary measures should be undertaken even if some aspects of the cause and effect relationship have not been scientifically established.[116] As might be surmised from the fact it is about to be replaced as the primary basis for drug approval, the precautionary principle is not universally accepted, in part due to the large variation in how it is applied.[117] Nevertheless, it is agreed to encompass three elements: the presence of scientific uncertainty, a significant threat of harm, and a set of possible precautionary actions to avoid such harm.[118] Its supporters view the principle as proactive and anticipatory, while its detractors as an unscientific evidentiary approach that impairs economic and technological progress based on unfounded or irrational fears.[119]

The focus of the debate over the precautionary principle as it relates to drug approval is (1) how to balance scientific uncertainty with risk in the context of inherently dangerous products and (2) who should bear the burden of adducing the required evidence of safety. Both issues are highly relevant for the lifecycle approach to approval: the former through risk acceptance and reallocation among public and private actors, and the latter through the shift in both the amount and, potentially, the type of scientific evidence required for drug approval, particularly in the context of expedited approval.[120] The question is an open one as to how best to move from a strong (100% evidence of safety) or even moderate (≥ 75% evidence of safety) precautionary principle to a benefit-risk analysis that expressly balances (≥ 51% evidence of safety) the public interest in health and safety with corporate efficiency considerations. In comparison, a purely economic focus on regulation is one that is

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112 Health Canada, "Priority Review", *supra* note 97 at i; *NOC/c Guidance Document*, *supra* note 104 at i.

113 *NOC/c Guidance Document*, *supra* note 104 at i ("[A]lternate approaches to the principles/practices outlined in the documents may be accepted if they are supported by adequate scientific justification").

114 Health Canada, "Drugs and Health Products—Special Access to Drugs", online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/acces/index-eng.php>.

115 *Food and Drugs Act*, *supra* note 3; *Food and Drug Regulations*, *supra* note 4.

116 Pauline Barrieu & Bernard Sinclair-Desgagné, "On Precautionary Policies" (2006) 52 Management Science 1145 at 1147.

117 Currently, there are between fourteen and nineteen different versions implemented globally: P. Sandin, "Dimensions of the Precautionary Principle" (1999) 5 Human and Ecological Risk Assessment 889; D. VanderZwaag, "The Precautionary Principle in Environmental Law and Policy: Elusive Rhetoric and First Embraces" (1998) 8 J. Envtl. L. & Prac. 355; Barrieu & Sinclair-Desgagné, *supra* note 116.

118 Carolyn Raffensperger & Joel Tickner, eds., *Protecting Public Health and the Environment: Implementing the Precautionary Principle* (Washington: Island Press, 1999).

119 Royal Society of Canada Expert Panel Report on the Future of Food Biotechnology, Elements of Precaution: Recommendations for the Regulation of Food Biotechnology in Canada" (2001) 64 Journal of Toxicology and Environmental Health 1 at 194.

120 Health Canada, "Blueprint", and Health Canada, "Concept Paper", *supra* note 23.

geared toward licensing products that meet minimum quality standards (e.g., positive benefit-risk ratio), rather than licensing products that are absolutely safe.[121]

In strong formulations of the precautionary principle, absolute proof of safety is necessary before allowing a certain activity. Pharmaceutical firms carry the legal burden of proof to introduce necessary and sufficient evidence of drug safety in their drug submissions. While this formulation accords with a government gate-keeping function, it is nevertheless parochial in nature and presents a significant hurdle for drug development and approval seen through the eyes of newer systems biology frameworks. As discussed in the context of regulated innovation ecologies,[122] systems-based mental models and analytical frameworks acknowledge the non-linear and uncertain nature of clinical research, even that which is conducted under the most controlled circumstances. The acceptance of uncertainty and risk in the context of medical product development and regulation clearly breaches the requirement in strong articulations of the principle for absolute proof *ex ante*. By contrast, weak articulations of the principle allow activities to be undertaken in the absence of any scientific proof at all[123] which also presents obvious and serious risks to human health. Moderate articulations of the principle open the door to some type of benefit-risk analysis while avoiding pitfalls associated with extremes of both positions.

The moderate position has been implicitly supported by the U.S. Institute of Medicine (IOM) in its *Future of Drug Safety* report.[124] The IOM expressly adopted a position that respects uncertainties involved in scientific investigation,[125] acknowledging that even the best drug safety system in the world will not prevent serious adverse reactions to marketed pharmaceuticals due in part to the complexity of their mechanisms of action. Probing the connection between post-market withdrawals and the effectiveness of drug regulation more generally, IOM noted that

> [s]ome observers believe that drug withdrawals (which are only one potential indicator of drug safety) represent de facto failures of the drug regulatory system, or that newly identified unusual and serious adverse events indicate that someone made a mistake in approving the drug. This is not so. FDA approval does not represent a lifetime guarantee of safety and efficacy, and what is newest is not always the best. For several related reasons, even the best drug safety system would not prevent adverse reactions to pharmaceuticals on the market. It is impossible to know everything about a drug at the point of approval because drugs' mechanisms of action are complex, and because the clinical testing that happens before approval is generally conducted in controlled settings in defined, carefully selected populations that may not fully represent the wide range of patients who will use the drug after approval, some chronically, and in combination with other drugs. Thus, the understanding of a drug's risk-benefit profile necessarily evolves over the drug's lifecycle. CDER staff who review regulatory submissions, such as new drug applications, must strike a delicate balance in judging the drug's risks and benefits, and whether the need for more study to increase certainty before approval warrants delaying the release of the drug into the marketplace and into the hands of health care providers and their patients.[126]

The FDA reformulated the nexus between the uncertainties of drug development and those of regulation, suggesting that the answer to the problem of post-marketing drug safety was the emerging "science of safety."[127] FDA clearly views this field as providing quantitative risk management methods not only to target drug use to specific patients but to provide a critical method to "prevent adverse effects by rapidly identifying drug safety problems before they can cause injury."[128] From the report, one might also surmise that FDA envisions a roping in of the uncertainties of drug development as

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121 Louis P. Garrison Jr., Adrian Towse & Brian W. Bresnahan, "Assessing a Structured, Quantitative Health Outcomes Approach to Drug Risk-Benefit Analysis" (2007) 26 Health Affairs 684 at 687.

122 Bouchard, "Systems", and Bouchard, "Reflections", *supra* note 69.

123 Kenneth R. Foster, Paolo Vecchia & Michael H. Repacholi, "Risk Management: Science and the Precautionary Principle" (2000) 288 Science 979 at 979.

124 *IOM Report*, *supra* note 8.

125 *Ibid.* at S-2; For general references regarding the role of uncertainty in scientific systems and daily life, see Gunther S. Stent, *Paradoxes of Progress* (San Francisco: W.H. Freeman, 1978); John L. Casti, *Searching For Certainty: What Scientists Can Know About the Future* (New York: William Morrow & Co., 1990); Paul W. Glimcher, *Decisions, Uncertainty and the Brain*: *The Science of Neuroeconomics* (Cambridge, MA: MIT Press, 2003).

126 *IOM Report*, *supra* note 8 at S-3.

127 U.S., Food and Drug Administration: Department of Health and Human Services, "The Future of Drug Safety—Promoting and Protecting the Health of the Public: FDA's Response to the Institute of Medicine's 2006 Report" (January 2007) at 3 (website on file with author) [FDA, "Response"].

128 *Ibid.*

the key to "the trade-off between safety and access" or indeed that between safety, access and industrial development. Mitigation of uncertainty via development of new quantitative tools is therefore seen by FDA as a legitimate tool for the agency to achieve its goals of "personalized, predictive, [and] preventive" medicine.[129] Contrary to first impression, FDA's position on the "science of safety" does not veer toward a stronger precautionary stance, notwithstanding the scientific, quantitative, or otherwise objective discourse in which it is embedded. This is because of FDA's explicit purpose to support its pharmaceutical partners and stimulate industrial innovation using corporate risk management tools, including the scenario where the "Agency's efforts to improve drug safety must not dampen the process of innovation that could itself enable safer approaches to drug development and drug use."[130] At no point does FDA stipulate or define what constitutes an acceptable or even desirable level of "innovation" from a societal perspective, let alone how the goal of facilitating innovation relates to the degree of acceptable risk tolerance by a technologically naïve drug-consuming public.

IOM's approach (if not that of FDA) is consistent in a number of respects to the work of the EMEA on benefit-risk assessment models.[131] Importantly, both advocate a "hybrid" or "semi-quantitative" benefit-risk assessment framework that incorporates objective evidence-based and subjective expertise-based decision-making methods. However, the EMEA Committee for Medicinal Products for Human Use (CHMP) has stipulated quite clearly that "quantitative benefit-risk assessment is not expected to replace qualitative evaluation" as the cornerstone of the drug approval process.[132] Rather, "expert judgment is expected to remain the cornerstone of benefit-risk evaluation for the authorization of medicinal products" for the foreseeable future. CHMP noted that to date none of the main global regulatory agencies have issued a list of benefit and risk criteria and that "there is no agreed approach on the methodology to estimate the overall benefit risk, and how to describe the way evidence is weighed and balanced."[133] Moreover, over-reliance on quantitative numerical models had the potential to skew benefit-risk calculations, because many quantitative models do not adequately reflect the "intellectual process of assessing the empirical evidence, accommodating risks and balancing risks and benefits."[134] After reviewing a number of quantitative, qualitative, and hybrid models, including the Number Needed to Treat (NNT), Number Needed to Harm (NNH), Principle of Three, Transparent Uniform Risk Benefit Overview (TURBO), and Multi-Criteria Decision Analysis (MCDA) models, CHMP concluded that hybrid models represented the best available decision-making approach to drug regulation based on their ability to balance objective risk assessment with expert judgment. In its follow-on report[135] the committee elaborated further on its reasons, highlighting the fact that MDCA and other hybrid models were best able to combine objective and subjective factors by allowing for uncertainties inherent to drug development and drug regulation as well as different stakeholder interests while minimizing the dangers of oversimplified quantitative models.[136] The committee called for enhanced transparency in regulatory decision-making,[137] largely via pressure on experts to explicitly document their reasons for subjective judgments and their selection of certain quantitative criteria over others and to recognize and account for differing stakeholder interests in approval.

In a recent review of emerging regulatory models, Eichler *et al.* also underscored the importance of various types of uncertainty in developing, regulating, and consuming novel therapeutic products.[138] Particular attention was drawn to the inherently unpredictable nature of these risks and their

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129 *Ibid.* at 4, 6, 8.
130 *Ibid.* at 3.
131 *EMEA CHMP 2* and *EMEA CHMP 3*, *supra* note 12. See also *EMEA Innovation, supra* note 9; *EMEA Road Map*, *supra* note 82. As noted in *EMEA CHMP 3* (at 3), the threshold for approval pursuant to Article 26 of Directive 2001/83 is that "market authorisation shall be refused if the benefit-risk balance is not considered to be favourable or if therapeutic efficacy is insufficiently substantiated."
132 *EMEA CHMP 2*, *supra* note 12 at 7.
133 *Ibid.* at 3.
134 *Ibid.* at 7.
135 *Ibid.* at 4-6.
136 *Ibid.* at 5.
137 *Ibid.*at 7, 13; *EMEA CHMP 3* at 2, 4, 5.
138 Eichler *et al.*, *supra* note 94.

relation to idiosyncratic, rare, or otherwise unexpected adverse drug reactions (ADRs). The authors stated that "ADRs are not likely to become a thing of the past, do not necessarily indicate failure of the regulatory process and have to be accepted in any model of drug approval - early or late."[139] Indeed, the notion that consumption of pharmaceutical products inevitably involves some form of risk and the public must assume a significant fraction of this risk, constitutes the main driver of emerging risk management models of drug regulation. Given the public outcry over drugs that have been withdrawn from the market for safety considerations,[140] it is not surprising that some drug agencies, including Health Canada, have come to an understanding that they must strike a delicate balance between providing the public with timely access to new drugs and adjudicating the risks and benefits of drug development under conditions that are uncertain and continually changing. Complicating this scenario is the information asymmetry that exists with regards to ADRs even when that information is available. The pervasive nature of the uncertainties combined with knowledge asymmetry has prompted numerous jurisdictions, including Canada,[141] the E.U.,[142] and the U.S.,[143] to base the regulatory exercise on both objective and subjective metrics rather than solely on objective evidence and quantitative models. For this reason, it seems reasonable to conclude that hybrid decision-making models embrace the more moderate articulation of the precautionary principle, even if it is reformulated in benefit-risk terms. Consequently, while the precautionary principle will no longer form the exclusive basis for drug approval, it seems premature to sound its death knell just yet.

D. IPR Rights Associated with Approval

In addition to changes in the speed and mechanism of review, there are subtle global and domestic economic forces driving the lifecycle debate that have attracted less attention.[144] For example, since 1993, there has been a substantial shift in the relationship between intellectual property rights associated with pharmaceutical products and regulatory approval of the drugs these patents were intended to protect. As part of Canada's obligations under NAFTA[145] and TRIPS,[146] provisions for compulsory licensing of pharmaceuticals in the *Patent Act*[147] were repealed and replaced with "linkage regulations" referred to as *NOC Regulations*.[148] These regulations tie patent protection for marketed pharmaceuticals to the drug approval process by enabling brand name pharmaceutical firms to list as many patents as are relevant to a marketed product on a patent register. For a generic firm to receive market authorization for that product, each patent on the register must be shown in litigation to be either invalid or not infringed. In this way, the number and scope of patents registered for a given Canadian reference product control entry of generic drugs into the market. Linkage regulations create a bifurcated role for government,[149] potentially constitutional in nature,[150] as public health

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139 *Ibid*. at 821.

140 For book-length treatments, see Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Alfred A. Knopf, 2003); Jerry Avorn, *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs* (New York: Alfred A. Knopf, 2004); Sheldon Krimsky, *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* (Lanham, MD: Rowman & Littlefield, 2003); Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What To Do About It* (New York: Random House, 2004); Jay S. Cohen, *Overdose: The Case Against the Drug Companies* (New York: Penguin, 2001).

141 Health Canada, "Blueprint", *supra* note 23.

142 *EMEA CHMP 2* and *EMEA CHMP 3*, *supra* note 12; *EMEA Innovation*, *supra* note 9.

143 *IOM Report*, *supra* note 8.

144 Bouchard, "Balancing", *supra*, note 16; Ron A. Bouchard & Trudo Lemmens, "Privatizing Biomedical Research—A 'Third Way'" (2008) 26 Nature Biotechnology 31 [Bouchard & Lemmens, "Biomedical"].

145 *North American Free Trade Agreement (NAFTA)*, 17 December 1992, Can. T.S. 1994 No. 2, 32 I.L.M. 289 (between the Governments of Canada, Mexico, and the United States; entered into force 1 January 1994).

146 *Trade Related aspects of Intellectual Property (TRIPS) 1994*, 30 October 1947, 58 U.N.T.S. 187, Can. T.S. 1947 No. 27 (negotiated as part of the Uruguay Round (1986-1994) of the World Trade Organization's General Agreement on Tariffs and Trade [GATT]).

147 R.S.C. 1985, c. P-4.

148 *Patented Medicines (Notice of Compliance) Regulations*, S.O.R./93-133. For a review of the history of the NOC Regulations, see Gunars K. Gaikis, "Pharmaceutical Patents in Canada: An Update on Compulsory Licensing" (1992) 42 Patent World 19; Edward Hore, "A Comparison of US and Canadian Laws as They Affect Generic Pharmaceutical Drug Entry" (1992) 55 Food & Drug L.J. 373.

149 See generally Rebecca S. Eisenberg, "Patents, Product Exclusivity, and Information Dissemination: How Law Directs

agencies are simultaneously charged with ensuring the safety and efficacy of pharmaceutical products while protecting the competitive advantage of firms. Patenting is seen to be critical in order for firms to innovate, and the quid pro quo accepted by domestic governments in this bargain appears to be the hope of new and useful products for consumers. The substance and procedure of the *NOC Regulations* were based on analogous legislation and policy in the U.S.[151] Prior to this point, patent protection and regulatory approval of pharmaceuticals were governed by two completely different statutes as well as different policy goals and objectives.[152] In addition to patent protection per se, new provisions were added to the *Food and Drug Regulations* pertaining to data, market and pediatric exclusivity. These exclusivity periods refer to periods of time, in addition to the patent monopoly, during which brand name sponsors are granted market monopolies linked to data submitted to Health Canada in the context of regulatory submissions.[153] Via amendments to C.08.004.1 of the *Food and Drug Regulations* in June 2006,[154] Canada provided for a guaranteed minimum period of 8.5 years of market exclusivity in order to implement its perceived NAFTA and TRIPS obligations. This includes six years of protection for regulatory submission data (data exclusivity), an additional two years of exclusivity (market exclusivity) during which an NOC cannot be issued to a generic manufacturer and an additional six months of protection to drugs that have been the subject of clinical trials in children (pediatric exclusivity). Hence, drugs approved by GOC are given substantial IPR rights which translate into multiple layers of market exclusivity.

Why the focus on IPR rights? To start with, it has long been understood that "large scale" commercialization[155] and appropriability[156] regimes are crucial for firms working within innovation-intensive industries.[157] This is particularly true for public policy having as its objective enhancement of national competitiveness and productivity via commercialization of publicly funded research,[158] which often singles out biomedical and life sciences sectors as fertile policy targets.[159] Indeed, it has been suggested that commercialization-based science and technology policies, legislation, and initia-

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Biopharmaceutical Research and Development (Edited version of Robert L. Levine Distinguished Lecture)" (2003) 72 Fordham L. Rev. 477; Bouchard, "Living", *supra* note 70.

150 Ron A. Bouchard, "Should Scientific Research in the Lead-up to Invention Vitiate Obviousness Under the Patented Medicines (Notice of Compliance) Regulations: To Test or Not to Test?" (2007) 6 C.J.L.T. 1 [Bouchard, "Test"].

151 *Drug Price Competition and Patent Term Restoration Act of 1984,* Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 USC § 355 (2000)), commonly known as the *Hatch-Waxman Act*.

152 *AstraZeneca Canada Inc. v Canada (Minister of Health)*, 2006 SCC 49, [2006] 2 S.C.R. 560 at para. 12 [*AstraZeneca*].

153 Lemmens & Bouchard, *supra* note 30 at 352. See also Regulations Amending the Patented Medicines (Notice of Compliance), C. Gaz. 2004.I.3719 (*Patent Act*); Regulations Amending the Patented Medicines (Notice of Compliance), C. Gaz. 1993.II.1388; and Regulations Amending the Patented Medicines (Notice of Compliance), C. Gaz. 2006.I.1611 (*Patent Act*).

154 Regulations Amending the Food and Drug Regulations (Data Protection), C. Gaz.2006.I.1598.

155 Commercialization being the process of introducing a new product into the market; the actual launch of which is the final stage and the invention of which is the beginning.

156 Appropriability being a party's ability to capture profits generated from their own inventions, or those of others, as governed and shaped by prevailing legal, regulatory, technological, and social capital factors.

157 See generally David J. Teece, "Profiting from Technological Innovation: Implications for Integration, Collaboration, Licensing and Public Policy" (1986) 15 Research Policy 285.

158 Institute for Competitiveness & Prosperity, *Reinventing Innovation and Commercialization Policy in Ontario,* Working Paper No. 6 (Toronto: Institute for Competitiveness & Prosperity, 2004) [*ICP Reinventing*]; Brian Guthrie & Trefor Munn-Venn, *Six Quick Hits for Canadian Commercialization: Leaders' Roundtable on Commercialization* (Ottawa: Conference Board of Canada, 2005) [*Guthrie & Munn-Venn*]; Government of Canada: Expert Panel on Commercialization, *People and Excellence: The Heart of Successful Commercialization* (Ottawa: Public Works and Government Services Canada, 2006) [*EPC Heart*]; Erika Fitzpatrick, *Innovation America: A Final Report* (Washington: National Governors Association, 2007) [*TCC Innovate*]; The Council on Competitiveness, *Innovate America: Thriving in a World of Challenge and Change* (Washington: The Council on Competitiveness, 2007); The Council on Competitiveness, *Five for the Future* (Washington: The Council on Competitiveness, 2007) [*TCC Five*].

159 Elias Zerhouni, "The NIH Roadmap" (2003) 302 Science 63; Alan Bernstein, "Toward Effective Canadian Public-Private Partnerships in Health Research" (2003) 168 Canadian Medical Association Journal 288; U.S., Food and Drug Administration: Department of Health and Human Services, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (2004), online: FDA <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf> [*NIH Innovation or Stagnation*]; Health Canada, "Blueprint", *supra* note 23; *EMEA Road Map, supra* note 82.

tives were responsible for stimulating the global biotechnology revolution.[160] Over the years however, this narrative has morphed from being focused on stimulating private innovation to discussions of publicly funded medical research and drug regulation. For example, intellectual property rights and pharmaceutical innovation comprise two of the five "pillars" of the nation's pharmaceutical policy[161] - three if one reasonably counts IPR rights as part of Canada's "international trade policy." The importance of IPR rights along with minimal intrusion into the drug regulation sphere also permeate Canada's National Pharmaceutical Strategy and Smart Regulations initiative,[162] both of which are intended to lay the policy grounds for enhancing national productivity and prosperity through commercialization of innovative medical research. Canada is not alone in this regard. Since the passage of the U.S. *Bayh-Dole Act*,[163] private IPR rights have evolved into a fundamental policy lever[164] for the entire rTPL innovation ecology;[165] a claim supported by the reading in of TRIPS rights into Bill C-51[166] and associated policy discussions.[167] Indeed, IPR rights have been touted increasingly throughout the E.U. as a linchpin not only for national science and technology policies, but also as a fundamental policy lever for governments to fulfill their public health mandate.[168]

Considerations such as these form a critical, though not widely understood, element of the "push-pull" dynamic in the pharmaceutical marketplace, which affects the number, quality and innovative nature of new drugs. A push-pull market system refers to movement of potential and realized therapeutic products between two poles, with "pull" referring to the various mechanisms by which consumers and agents of consumers enhance demand for a given product, and "push" referring to the mechanisms by which suppliers, and agents of suppliers, direct products toward consumers. It is by no means clear just how distinct and separate the various segments of government, public and pharmaceutical players are from one another and their respective agendas. In the context of drug regulation, the term "access" is theoretically an excellent proxy for consumer pull, while push largely refers to the regulatory mechanisms underpinning the production and market protection of products that are "safe and efficacious". However, depending on the degree of overlap and interrelation of

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160 Bhavan N. Sampat, "Patenting and US Academic Research in the 20th Century: The World Before and After Bayh-Dole" (2006) 35 Research Policy 772 at 777; Bouchard, "Test", *supra* note 150.

161 According to GOC, the five "pillars" of federal pharmaceutical policy are the following: (1) intellectual property, (2) pharmaceutical research and development, (3) international trade policy, (4) health care and (5) consumer protection: Barbara Oullet, "Pharmaceutical Management and Price Control in Canada" (Presentation to the North American Pharmaceutical Summit, 31 March 2006) at 7.

162 *National Pharmaceuticals Strategy*, *supra* note 13; *Smart Regulations*, *supra* note 14; Government of Canada, "Cabinet Directive on Streamlining Regulation" (2007), online: Government of Canada <http://www.regulation.gc.ca/directive/directive00-eng.asp> (Specifically, the National Pharmaceutical Strategy states [at 39] "Governments recognize the crucial role the innovative pharmaceutical industry plays in the development of breakthrough drugs and that intellectual property protection is key to encouraging and supporting innovation").

163 *Bayh-Dole Act*, 35 U.S.C. §§ 200-212 (1994). See also *Stevenson-Wydler Technology Innovation Act of 1980*, 15 U.S.C. §§ 3701-3715 (2000); *Federal Technology Transfer Act of 1986*, 15 U.S.C. §§ 3710a-3710d (2000).

164 Dan L. Burk & Mark A. Lemley, "Policy Levers in Patent Law" (2003) 89 Va. L. Rev. 1575 at 1591. See also Sampat, *supra* note 160; Donald E. Stokes, *Pasteur's Quadrant: Basic Science and Technological Innovation* (Washington: Brookings Institution Press, 1997).

165 See both Wulf, and Bouchard, "Systems", *supra* note 69.

166 *Bill C-51*, *supra* note 10 at cl. 11 s. 30(3).

167 Peterson, *supra* note 15.

168 For example, the *EMEA Road Map* (*supra* note 82 at 2, 36) stipulates that the agency uses a "two-pillar approach" to make safe and effective therapeutic products available to the public. They are to (1) facilitate more rapid access to safe and effective medicines via amendment to the existing regulatory licensing framework and to (2) facilitate industrial innovation. While EMEA does not provide a definition of "innovation" nor a "map" of how it will facilitate innovative drug development in its road map or follow-up report (European Medicines Agency, *Second Status Report on the Implementation of the EMEA Road Map (Doc. Ref. EMEA/359050/2007)* [22 October 2007]), it can be plausibly assumed at the main economic drivers for this process will be a combination of intellectual property and regulatory rights. Citing EMEA Road Map, Eichler *et al.* (*supra* note 94 at 2) point out that "regulators acknowledge the need to facilitate innovation and the fact that a lack of efficacious therapies *is a public health issue*" [Emphasis added]. For a review of how drug development is seen to be necessarily contingent on the nexus between technology commercialization and IPR rights, see generally *NIH Innovation or Stagnation, supra* note 159; Mark Ratner, "Looking for Solid Ground Along the Critical Path" (2006) 24 Nature Biotechnology 885; S. Buckman, S.M. Huang & S. Murphy, "Medical Product Development and Regulatory Science for the 21st Century: The Critical Path Vision and Its Impact on Health Care" (2007) 81 Clinical Pharmacology & Therapeutics 141 [Buckman *et al.*]; "NIH at the Crossroads", Editorial, (2003) 425 Nature 545; R.L. Woosley & J. Cossman "Drug Development and the FDA's Critical Path Initiative" (2007) 81 Clinical Pharmacology & Therapeutics 129; Zerhouni, *supra* note 159; Bernstein, *supra* note 159.

consumers, government, and industry actors, the economic and public policy levers underpinning access to and the production of safe and efficacious drugs will be fundamentally intertwined. As a result, the desire for strong IPR rights permeates the entire push-pull dynamic, particularly since both patent and regulatory rights are now seen to constitute critical economic levers in the global production of innovative therapeutic products. One implication of the global nature of emerging models of drug legislation is that multinational firms seeking to market innovative products might see Canada in a negative light to the extent that domestic IPR rights are out of line with those more globally.[169] This implies the rTPL-IPR rights nexus will only tighten as GOC shifts from its current drug approval framework to the PLF lifecycle model, in turn strengthening market penetration by pharmaceutical/biotechnology players that have learned to master both linkage regulation loopholes[170] and invention by investment portfolio strategies.[171]

The result of this scenario is that arguments about "access," particularly those that are contingent on claims for strong IPR rights, are less about *demand* for safe and efficacious drugs than they are about market *push* mechanisms. This raises the specter of post-marketing safety and whether inclusion of yet further grounds for expedited review in emerging lifecycle models will, or even can be counter-balanced by appropriate post-marketing surveillance. GOC has been reasonably transparent about the priority of this balancing function in its policy documents[172] and legislative package,[173] going so far as to say in its PLF Concept Paper that under certain circumstances the potential benefits of bringing a drug to market may be "deemed to outweigh the relatively increased uncertainty regarding the safety and efficacy."[174]

E. Post-Approval Safety

There is varying evidence as to whether the shifts in the speed and mechanisms underpinning regulatory approval are positively correlated with increased post-marketing safety problems,[175] in particular drug withdrawals.[176] Several reports have claimed that there is no significant increase in the incidence of withdrawals, dosage form discontinuations, or black-box warnings before and after initiation of user fees in the U.S.,[177] while others have demonstrated a significant[178] or even substan-

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169 Ron A. Bouchard, "KSR v. Teleflex Part 1: Impact of U.S Supreme Court Patent Law on Canadian Intellectual Property and Regulatory Rights Landscape" (2008) 15 Health L.J. 222.

170 *AstraZeneca*, *supra* note 152.

171 William Kingston, "Intellectual Property's Problems: How Far is the U.S. Constitution to Blame?" (2002) 4 Intellectual Property Quarterly 315 at 323.

172 Of the five objectives of the 2001 regulatory reform of the Food and Drug Regulations respecting clinical trials, three were aimed at reducing the costs of regulatory approval and facilitating innovation in the pharmaceutical industry. The objectives were to (i) shorten application review times without endangering health and safety, (ii) remove obstacles to firm research and development, (iii) improve access to innovative therapies, (iv) increase involvement of the regulator in clinical trials and follow-up, and (v) improve safety mechanisms for research subjects. See Health Canada, "Stakeholder Workshop", *supra* note 30.

173 *Bill C-51*, *supra* note 10 at cl. 11 s. 30(3) and cl. 13 30(7)(b).

174 Health Canada, "Concept Paper", *supra* note 23 at 20-1. The full quotation is "When a manufacturer is considering departing from the baseline requirement for substantial evidence of efficacy and safety for initial market authorization, a more flexible approach regarding the underlying efficacy and safety evidence is envisaged when there is a compelling reason. While the regulatory requirement for a favourable benefit-risk profile for the drug's use under the proposed conditions would remain, initial requirements for substantial evidence of efficacy and safety may be counterbalanced against other, important evidence concerning contextual benefit-risk considerations. For example, the potential benefits of bringing the drug to market are deemed to outweigh the relatively increased uncertainty regarding the safety and efficacy."

175 For review, see the following at *supra* note 140: Hilts; Avorn; Krimsky; Angell; and Cohen.

176 These studies are difficult to compare directly owing to substantial differences in methodologies used. Some authors use only data from industry organizations (Rx&D, PhRMA), while others use government and other publicly available databases, literature comparisons, commercial databases or reports, personal communications, or some combination of the above. In addition, some studies are long-term while others are short-term, and still others review withdrawals in the same or longer test period as approvals were issued. The situation has not been helped by the recalcitrance of federal drug agencies to provide withdrawal data in an easy to access form: Lexchin, "Withdrawals", *supra* note 74; Carpenter *et al.*, *supra* note 78.

177 *USGAO User Fees*, *supra* note 79 at 4, 24-26; Olav M. Bakke *et al.*, "Drug Safety Discontinuations in the United Kingdom, the United States and Spain from 1974 through 1993: A Regulatory Perspective" (1995) 58 Clinical Pharmacology & Therapeutics 108; Amalia M. Issa *et al.*, "Drug Withdrawals in the United States: A Systematic Review of the Evidence and Analysis of Trends" (2007) 2 Current Drug Safety 177; M.K. Olson, "Pharmaceutical Policy Change and the Safety of New

tial[179] increase. Independent of the literature, however, is the high level of publicly reported mortality and morbidity associated with safety withdrawals in vulnerable segments of the population. For this reason, the withdrawal of Vioxx has been described by *Nature* as the "biggest drug safety catastrophe in the history of the United States."[180] One might argue that even the COX-2 scenario pales to the damage done by SSRIs to vulnerable children and adolescents, which the *Lancet* referred to as a "disaster" for evidence-based medicine.[181]

Implementation of a fee-for-service basis for drug approval has been argued to affect drug safety in several ways.[182] First, many drugs are approved on the basis of surrogate rather than therapeutic end-points, including the wide use of biomarkers.[183] A biomarker is "a laboratory measurement that reflects the activity of a disease process,"[184] whereas a surrogate marker is "a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy."[185] The difference between the two is that a biomarker is a candidate surrogate marker, whereas a surrogate marker is a demonstrably testable and thus relatively more practical measure of the effects of a specific treatment.[186] Even so, a surrogate endpoint still represents a secondary measure of the effect of an experimental treatment which *may* correlate with an actual, or primary endpoint but does not necessarily have a guaranteed relationship with it (think the difference between a desired and likely endpoint of a year in the gym). Given the uncertainties involved in the use of surrogate markers it is not surprising that dependence on secondary rather than primary endpoints is claimed to enhance post-marketing risk for consumers.[187] Indeed, some have gone so far as to say the history of wide surrogate marker use is a "troubled one."[188] A second manner in which user fees are said to be problematic is the narrow employment thereof by regulators largely in the pre-market phase. Although the restriction of utilizing user fees to fund post-marketing safety as-

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Drugs" (2002) 45 J.L. & Econ. 615 [Olson, "Change"]; Rawson, *supra* note 89; Berndt *et al.*, *supra* note 78; U.S., Food and Drug Administration, *Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications* (November 2005) at 6, online: FDA <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119253.htm>; M. McClellan, "Drug Safety Reform at the FDA—Pendulum Swing or Systematic Improvement?" (2007) 356 New Eng. J. Med. 1700.

178 Carpenter *et al.*, *supra* note 78.

179 Diane K. Wysowski & Lynette Swartz, "Adverse Drug Event Surveillance and Drug Withdrawals in the United States, 1969-2002" (2005) 165 Archives of Internal Medicine 1363; Andrea Clarke, Jonathan J. Deeks & Saad A.W. Shakir, "An Assessment of the Publicly Disseminated Evidence of Safety Used in Decisions to Withdraw Medical Products from the UK and US Markets" (2006) 29 Drug Safety 175 [Clarke, Deeks & Shakir]; Carpenter *et al.*, *supra* note 78.

180 M. Wadman, "Drug Safety Special: The Safety Catch" (2005) 434 Nature 554 at 556.

181 "Depressing Research", editorial (2004) 363 The Lancet 1341.

182 Horton, *supra* note 74; Avorn, *supra* note 140; P. Lurie & L.D. Sasich, "Safety of FDA-Approved Drugs" (1999) 282 Journal of the American Medical Association 2297; John Abraham & Courtney Davis, "A Comparative Analysis of Drug Safety Withdrawals in the UK and the US (1971-1992): Implications for Current Regulatory Thinking and Policy" (2005) 61 Social Science & Medicine 881; *USGAO User Fees*, *supra* note 79 at 2, 4, 26-27; U.S., Office of Inspector General, *FDA's Review Process for New Drug Applications: A Management Review*, (Washington: Department of Health and Human Services, March 2003); S. Okie, "What Ails the FDA?" (2005) 352 New Eng. J. Med. 1063; Sheila Weiss Smith, "Sidelining Safety—The FDA's Inadequate Response to the IOM" (2007) 357 New Eng. J. Med. 961.

183 Eichler *et al.*, *supra* note 94 at 825. Aloka G. Chakravarty, "Surrogate Marker and its Role in the Regulatory Decision Process" (Powerpoint presentation) online: American Statistical Association <http://amstat.org/meetings/fdaworkshop/presentations/2004/ParallelSession6/ParallelSession6B.ppt> (Dr. Chakravarty, Deputy Director, Division of Biometrics III defines a "biomarker" as a "characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention").

184 Russell Katz, "Biomarkers and Surrogate Markers: An FDA Perspective" (2004) 1 NeuroRx 189 at 189.

185 *Ibid.* at 189; Robert Temple, "Are Surrogate Markers Adequate to Assess Cardiovascular Disease Drugs?" (1999) 282 Journal of the American Medical Association 790. See also J.N. Cohn, "Introduction to Surrogate Markers" (2004) 109 Circulation IV-20.

186 Katz, *supra* note 184 at 189.

187 Weiss Smith, *supra* note 182 at 961.

188 Eichler *et al.*, *supra* note 94 at 3, 8. The authors state (at 8): "While we are optimistic about the impact of new biomarkers for drug candidate selection, theranostic purposes or safety screening, we do not predict wider use of biomarkers as surrogate end points to accelerate marketing authorization … " The term "theranostic" refers to treatment modalities combining a diagnostic test with targeted therapy based on results from individual tests. The term is usually invoked in discussions of developing tailored therapies for individual patients in the context of personalized medicine.

sessments was lifted in 2002, this route continues to be used only in very limited circumstances,[189] to the potential detriment of end-users. Finally, the requirement for expedited approval for a drug candidate to be "potentially life-saving" has been very broadly interpreted in the context of expedited review, in turn giving rise to faster access for drugs intended to treat a variety of common chronic conditions, many of which were subsequently withdrawn for safety reasons.[190] As such, expedited review may not be a viable option for drugs intended to treat chronic conditions, which should have safety standards that tolerate minimal uncertainty.

The nuances of the debate over access are clouded by the fact that firms themselves are the primary capital sources for clinical trials, a situation that may lend itself to systemic bias in trial interpretation.[191] Firms own data obtained from clinical trials,[192] which is in any event deemed to be confidential information under domestic and international regulatory instruments.[193] Indeed, the pharmaceutical industry has gone to great lengths to protect the proprietary nature of such information.[194] For this reason, and in light of the scope of injury linked to recent safety withdrawals, there have been growing calls for enhanced transparency and independent review of pre-market and post-market drug efficacy and safety studies.[195] Indeed, the current emphasis on post-market surveillance has largely grown out of this debate. Moreover, various types of domestic and international patient advocacy groups now receive substantial funding from industry. It is therefore not surprising that concerns over transparency have been expressed in the U.S., Canada, Britain, Ireland, Italy, Germany, and elsewhere.[196] Typical of this type of conflict of interest is the recent "Patient Declaration on Medical Innovation and Access" submitted to the WHO with regard to its efforts to meet the public health needs of developing nations. Over half (61/110) of the document's signatories had financial ties with industry, including in Canada.[197] The biggest question, however, remains whether the reduction in approval times is correlated with the recent spate of high profile drug withdrawals.

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189 Weiss Smith, *supra* note 182 at 961-62.

190 *Ibid.* at 961.

191 Joel Lexchin *et al.*, "Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review" (2003) 326 British Medical Journal 1167. See also A.J.J. Wood, C.M. Stein & R. Woosley, "Making Medicines Safer: The Need for an Independent Drug Safety Board" (1998) 339 New Eng. J. Med. 1851; Krimsky, *supra* note 140 at 229; Angell, *supra* note 140 at 244-47; Wayne A. Ray & C. Michael Stein, "Reform of Drug Regulation—Beyond an Independent Drug-Safety Board" (2006) 354 New Eng. J. Med. 194 [Ray & Stein]; Cohen, *supra* note 140 at 198-211.

192 Thomas O. McGarity & Sidney A. Shapiro, "The Trade Secret Status of Health and Safety Testing Information: Reforming Agency Disclosure Policies" (1980) 93 Harvard L. Rev. 837; Jeffery M. Drazen, "Who Owns the Data in a Clinical Trial?" (2002) 8 Science and Engineering Ethics 407.

193 In Canada, data submitted by pharmaceutical companies is deemed to be "commercially sensitive" and as such constitutes confidential information under the federal *Access to Information Act* (R.S.C. 1985, c. A-1). Under section 20(6), disclosure can only be made where it is in the public interest and relates to public health and safety. The TPD will not however release information where public interest in disclosure is outweighed by financial loss or prejudice to the competitive position of the disclosing party. See also Article 1711 of NAFTA, *supra* note 145, and Article 39 of TRIPS, *supra* note 146, pertaining to data and market exclusivity, which deem commercially sensitive information to be confidential. See generally Regulatory Impact Analysis Statement, C. Gaz. 2004.II.3718 (Regulations Amending the Food and Drug Regulations [1390 - Data Protection]), as modified by Regulatory Impact Analysis Statement, C. Gaz. 2006.I.1598 (Regulations Amending the Food and Drug Regulations [Data Protection]).

194 For a detailed history of litigation over public disclosure of pharmaceutical R&D costs, see generally: U.S., Congress Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards* (Washington: U.S. Government Printing Office, 1993) at ii, 66, 284-288. The U.S. Supreme Court, in the seminal *Bowsher v. Merck* decision (*Bowsher v. Merck & Co. Inc.*, 460 U.S. 824 at 843, 103 S. Ct. 1587 at 1598 (1983)) held that pharmaceutical R&D, and related costs, constituted confidential information and thus that federal government did not have authority to compel disclosure of such information. For a more recent discussion of pharmaceutical R&D costs, see: U.S. National Institutes of Health, *NIH Response to Conference Report Request for Plan to Ensure Taxpayer's Interests are Protected* (Bethesda, MD: National Institutes of Health, 2001).

195 Weiss Smith, *supra* note 182; Bruce M. Psaty & Alta Charo, "FDA Responds to Institute of Medicine Drug Safety Recommendations—In Part" (2007) 297 Journal of the American Medical Association 1917; Ray & Stein, *supra* note 191.

196 See generally (and references therein): Daniel Carpenter, "The Political Economy of FDA Drug Review: Processing, Politics, and Lessons for Policy" (2004) 23 Health Affairs 52; Barbara Mintzes, "Should Patient Groups Accept Money From Drug Companies? No" (2007) 334 British Medical Journal 935.

197 Sarah Rimmington & Robert Weissman, News Release, "Signers of 'Patient Declaration' for WHO Talks Financially Tied to Big Pharma" (28 April 2008), online: Essential Information <http://www.essentialaction.org/access/index.php?/archives/141-News-Release-Signers-of-Patient-Declaration-for-WHO-talks-financially-tied-to-Big-Pharma.html>.

Despite the severity of recent withdrawals, a number of influential studies have found evidence to support the conclusion that serious post-market safety metrics, including drug withdrawals, dosage form discontinuations, and black-box warnings have not increased significantly following PDUFA. For example, Berndt *et al.*[198] conducted a detailed statistical analysis of the impact of PDUFA on approval times and withdrawal rates. Going beyond proportion comparisons to include Kaplan-Meier survival analysis,[199] they found that new molecular entities submitted to FDA before PDUFA (365; 1980-1992) had a 98% survival rate (2% withdrawal) compared with post-PDUFA I submissions (351; 1992-2003), which had a 97.1% survival rate (2.9% withdrawn). These data compare favourably with those of GAO[200] demonstrating that 3.10% of new medical entities approved between 1985 and 1992 were withdrawn for safety considerations compared to 3.47% during the period 1993-2000, a result that was not statistically different. Data from GAO and the Berndt study are consistent with other reports demonstrating a lack of change in the frequency of post-market black-box warnings (1981-2006)[201] and withdrawal rates (1993-2006)[202] before and after PDUFA I-III. While faster review did not, at least according to these reports, impact significantly on drug withdrawals or black-box warnings, there is evidence to support the conclusion that post-PDUFA withdrawals are occurring more rapidly.[203] A potential explanation for this trend is that pharmaceutical sales have "accelerated forward" in time, which may also explain the apparent increase in mortality and morbidity associated with high profile withdrawals in light of the disconnect between the characteristics of clinical trial populations and the consuming public. Other studies focusing on post-market safety issues such as withdrawal rates[204] and adverse effects[205] found no substantial change before and after the institution of user fees, with one study demonstrating a transient increase in withdrawal rates during the 1990s that tailed off following the year 2000.[206]

However, not all reports agree with the conclusion that PDUFA has had no significant effect on post-market safety metrics. A recent empirical study by Carpenter, Zucker, and Avorn[207] suggested that PDUFA-imposed decision deadlines were associated with an increased incidence of black-box warnings, discontinuation of at least one dosage form and subsequent drug withdrawals for safety reasons, particularly for approvals in the 2 months prior to the deadline. Of the 11 drugs withdrawn for safety reasons in the period 1993-2004 (average, 0.92.yr or 3.5% of 313 new molecular entities), 7 were for drugs approved just before the PDUFA-imposed deadline. In a reply,[208] FDA disputed these data, stipulating that only 5 of 11 approvals were withdrawn close to the deadline. In their response,[209] the authors argued that FDA used data never before reported, but even so that their conclusions were not altered. They further concluded that PDUFA-imposed deadlines rather than the speed of approval per se were responsible for the increase in observed withdrawals,[210] pointing out that their data were consistent with reports from FDA

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198 Berndt *et al.*, *supra* note 78 at 552.

199 Berndt *et al.* (*ibid.* at 558) state that the Kaplan-Meier survival function utilized in their study measures "the percentage of subjects in a cohort that survive from one time period to the next." As pointed out by the authors, the Kaplan-Meier method takes into account "censored" data, referring to the loss or censoring of data from the sample prior to finalization of the data set. This outcome is very useful where, as can often be the case for large and complex data sets such as those involving drug approvals or post-market safety metrics such as drug withdrawals, black box warnings or dosage form discontinuations, not all data is reliably reported by regulators (see for example, the report on drug withdrawals by Carpenter *et al.*, the FDA's response to it, and the authors' subsequent reply: Carpenter *et al. supra* note 78; Nardinelli *et al.*, *supra* note 94; Reply to Letter to Editors, *supra* note 94).

200 *USGAO User Fees*, *supra* note 79 at 25-26.

201 Allan Begosh *et al.*, "Black Box Warnings and Drug Safety: Examining the Determinants and Timing of FDA Warning Labels" (2006) NBER Working Paper 12803; Henry G. Grabowski & Y. Richard Wang, "The Quantity and Quality of Worldwide New Drug Introductions 1982–2003" (2006) 25 Health Affairs 452.

202 Issa *et al., supra* note 177.

203 Berndt *et al.*, *supra* note 78 at 553.

204 Michael A. Friedman *et al.*, "The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There is A Problem?" (1999) 281 Journal of the American Medical Association 1728.

205 Henry G. Grabowski & Y. Richard Wang, "Do Faster Food and Drug Administration Drug Reviews Adversely Affect Patient Safety? An Analysis of the 1992 Prescription Drug User Fee Act" (2008) 51 J.L. & Econ. 377.

206 Tufts Center for the Study of Drug Development, "Drug Safety Withdrawals in the US Not Linked to Speed of FDA Approval" (2005) 7 Tufts CSDD Impact Report 1 at 2 [Tufts Center].

207 Carpenter *et al.*, *supra* note 78.

208 Nardinelli *et al.*, *supra* note 94 at 95.

209 Carpenter "Reply", *supra* note 94 at 97-98.

210 Carpenter *et al., supra* note 78 at 1357-58.

scientists[211] that PDUFA has reduced the agency's focus on risks and refocused it on benefits.[212] The data of Carpenter *et al.* are consistent with the results of a large-scale study by Abraham and Davis[213] comparing drug withdrawals in the U.K. and U.S. during the period 1971-1992. The conclusion of this study was that acceleration of review times, rather than several other alternatives, was correlated with increased drug safety withdrawals in the U.K. (22/21 years, or 1.05/yr) compared to the U.S. (9/22 years, or 0.43/yr) before PDUFA. A recent study by Olson,[214] controlling for the influence of drug utilization, patient conditions, drug novelty, black-box warnings, foreign drug launch, U.S. launch lags, as well as patient age and gender, found a positive correlation between faster review times and serious ADRs during the period 1990-2001, particularly for more novel drugs. A reduction in review time by a single standard deviation was estimated to result on average in a ~20% increase in serious ADRs, ADR-related hospitalizations, and ADR-related deaths. Other studies have demonstrated higher average withdrawal rates in the years following PDUFA[215] compared to those in preceding years.[216]

In Canada, Lexchin reported a total of 41 withdrawals for safety reasons over the period 1963-2004,[217] amounting to an average withdrawal rate of about 1/year. Hepatotoxicity, cardiac problems, and blood dyscrasias (arrhythmias, vascular disorders, hemolytic anemia, and agranulocytosis) were the leading causes for withdrawal. Withdrawals in 10 year bins for the period 1963-2004 were 10, 6, 7, and 16, respectively,[218] with a further 8 in the greatly abbreviated 2004-2007 bin.[219] While it is tempting to speculate that there is a positive correlation between the sharp increase in withdrawals post-PDUFA I, other data from the author suggest there has actually been a *decrease* in withdrawals expressed as 5 year bins between 1985-2007 when graphed against the number of new active substances (NAS) approved.[220] This parallels recent data from Issa *et al.*[221] demonstrating an average withdrawal rate of 1.5/year between 1993-2006 and a lack of change in average withdrawals before and after PDUFA I and II (1975-1992 v. 1993-2006), though the data do appear to show trends toward escalating withdrawal rates between 1995-2000 and 2001-2006 expressed either as absolute values or as a percentage of approved drugs.[222] The average withdrawal rates in these two studies compares favourably with those from similar longer-term analyses in the U.K. (1.05/yr, 1971-1992;[223] 1.0/yr 1970-1992[224]), Germany (1.3/yr, 1970-1992[225]) and France (1.35/yr, 1970-1992) that were conducted prior to PDUFA. Other studies, however, reported comparatively lower U.S. withdrawal rates over the same or similar timeframes (0.3/yr, 1970-1992;[226] 0.43/yr, 1971-1992;[227] 0.5, 1978-1992;[228] 0.64/yr, 1975-1999[229]).

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211 Union of Concerned Scientists, "Voices of Scientists at FDA: Protecting Public Health Depends on Independent Science" (Cambridge, MA: Union of Concerned Scientists, 2006), online: Union of Concerned Scientists <http://www.ucsusa.org/assets/documents/scientific_integrity/fda-survey-brochure.pdf>; David B. Ross, "The FDA and the Case of Ketek" (2007) 356 New Eng. J. Med. 1601. See also Okie, *supra* note 173; Gardiner Harris, "FDA Scientists Accuse Agency Officials of Misconduct" *New York Times* (18 November, 2008) (describing a letter sent by FDA scientists on October 14, 2008 to Congress alleging FDA is engaged in "serious misconduct" by approving unsafe or ineffective medications) at A15 [Harris, "Accuse"].

212 Weiss Smith, *supra* note 182; *PDUFA*, *supr*a note 72.

213 Abraham & Davis, *supra* note 182.

214 Mary K. Olson, "The Risk We Bear: The Effects of Review Speed and Industry User Fees on New Drug Safety" (2008) 27 Journal of Health Economics 175 [Olson, "Risk"]. See also Olson, "Change"*, supra* note 177.

215 Wysowski & Swartz, *supra* note 179; Rawson & Kaitin, *supra* note 81; Issa *et al.*, and Olson, "Change", *supra* note 177; Clarke, Deeks & Shakir, *supra* note 179.

216 Sidney M. Wolfe, "Differences in the Number of Drug Safety Withdrawals: United States, United Kingdom, Germany, France 1970-1992" Public Citizen, Health Research Group Paper (2 February 1995); Abraham & Davis, *supra* note 182; Wysowski & Swartz, *supra* note 179 (see also Tables 3 and 4 therein at 1366-67); Karen E. Lasser *et al.*, "Timing of New Black Box Warnings and Withdrawals for Prescription Medications" (2002) 287 Journal of the American Medical Association 2215 [Lasser *et al.*].

217 Lexchin, "Withdrawals", *supra* note 74 at 765.

218 *Ibid.*

219 Joel Lexchin, Personal Communication (September 24, 2008).

220 Joel Lexchin, Personal Communication (October 2, 2008).

221 Issa *et al.*, *supra* note 177.

222 *Ibid.* at 180-182 (particularly, Figs. 1-3).

223 Abraham & Davis, *supra* note 182.

224 Wolfe, *supra* note 216.

225 *Ibid.*

226 *Ibid.*

These findings contrast somewhat with data reported by Rawson and Kaitin,[230] who found that there were about 2.4x more drug withdrawals in the U.S. compared with Canada during the period 1992-2001 assessed either as the average number of withdrawals per year (0.6/yr v. 1.2/yr) or as a per cent of total approvals (1.7% of 295 approvals v. 3.56% of 337 approvals). U.S. regulators approved 15% more new chemical entities, 82% of which were also approved in Canada, and approved them about 30% faster than their Canadian counterparts.[231] Moreover, and perhaps accounting (along with a much shorter and more recent test period)[232] for differences in their data and those of Lexchin, there were 2.2x more priority reviews in the U.S. than in Canada over the test period. The authors concluded that Canadian regulators may have avoided potential dangers owing to longer approval times, a conclusion applied earlier under opposite conditions to U.S. regulators in a comparative study of drug withdrawals in the U.S. and U.K. during the two decades leading up to PDUFA I.[233]

Despite the strength of the statistical methods brought to bear on the analyses discussed above, one must nevertheless be cautious in relying on differences in average withdrawal or black-box warning rates, as these will be subject to variation owing to stochastic noise in the approval processes from one year to the next. In addition, pre-market decisions are based on benefit-risk calculations where a drug's benefits need only "outweigh" its risks and even then in an artificially narrow clinical trial population that has been selected to hit desired safety or efficacy signals. For the same reason, "off-label use" for example, physicians prescribing for non-approved uses, is also problematic. Moreover, as discussed by Lexchin,[234] and more recently by Berndt,[235] Carpenter,[236] and others,[237] adverse effects that are rare, idiosyncratic, or even unpredictable (and thus difficult or impossible to control under typical clinical trial constraints) can nevertheless be found to cause profound adverse effects under post-market scrutiny,[238] as observed with selective cyclooxygenase isoenzyme (e.g., COX-2) inhibitors, selective serotonin reuptake inhibitors (SSRIs), cisapride, rosiglitazone, statins, tegaserod, gefitinib, terfenadine, and telithromycin, among others. In light of the confusion over how to interpret the consequences of high profile withdrawals of drugs that appear to be consumed by an increasing percentage of the public at an increasing rate, the question we are left with is how to balance the obvious need for an approval regime that will minimize consequences such as these with the need for caution in its implementation. From the above discussion, the factors that need to be balanced and weighed in evolving regulatory models include those in Table 1 below.

TABLE 1. FACTORS BALANCED IN EMERGING MODELS OF DRUG REGULATION

o Public Health Protection	o Innovation and Economic Development
o Government as Fiduciary	o Government as Facilitator of Choice
o Safety and Efficacy	o Access
o Certainty	o Uncertainty
o Objectivity	o Subjectivity
o Formal Decision-Making Model	o Contextual Decision-Making Model
o Precautionary Principle	o Risk Management
o Transparency	o Black-Box
o Publicly-Funded Medical Research	o Private IPR Rights

227 Abraham & Davis, *supra* note 182.
228 Wysowski & Swartz, *supra* note 179.
229 Lasser *et al.*, *supra* note 216.
230 Rawson & Kaitin, *supra* note 81 at 1404.
231 *Ibid.* Re-calculated as the mean of data reported by Rawson and Kaitlin for the years 1993, 1997, and 2000.
232 A review of the reported literature suggests that studies with shorter test periods that are closer to the present date tend to yield much higher average withdrawal rates per year compared to test periods that are longer in length and prior to PDUFA I.
233 Abraham & Davis, *supra* note 182.
234 Lexchin, "Withdrawal", *supra* note 74 at 766.
235 Berndt *et al.*, *supra* note 78 at 551.
236 Carpenter *et al.*, *supra* note 78.
237 Eichler *et al.*, *supra* note 94; Issa *et al.*, *supra* note 177; Olson, "Risk", *supra* note 214. For an earlier discussion of the same problem, see: *USGAO User Fees, supra* note 79 at 26.
238 See also Issa *et al.*, and Olson, "Change", *supra* note 177; Olson, "Risk", *supra* note 214.

F. Lifecycle Approach

1. *Canada*

It has become the role of the "lifecycle approach" to drug regulation to balance the opposing factors listed in Table 1, particularly the tension between access and safety.[239] As reviewed *supra*, one of the largest problems facing drug regulators, acknowledged expressly by GOC in light of escalating high profile post-market withdrawals,[240] is that not enough focus is placed on the safety and efficacy of pharmaceuticals following market authorization. In its progressive licensing framework Concept Paper, GOC states that "while the traditional pre-market evaluation of a drug has worked dependably as a system for many years, it does not identify all the significant information about drug benefits and risks."[241] Despite the requirement by GOC for drug manufacturers to adhere to certain obligations following a drug's market authorization (reporting of adverse events, updating safety information, maintaining drug quality to appropriate standards, and application for further authorization for significant changes to the product), the existing *Food and Drugs Act* and regulations provide limited jurisdiction and very few regulatory tools to ensure compliance with even these minimal obligations. Moreover, outside of the NOC/*c* stream, there are no legal grounds to impose additional systematic long-term safety and efficacy studies as a condition of continued marketing or when new information suggests that additional research is warranted.[242] As such, the current regulatory regime is strongly front-loaded[243] in that the vast majority of regulatory resources are spent before initial market authorization, when very little information is known, and almost none following market entry when the vast majority of information pertaining to drug safety and efficacy becomes available.[244]

The circumstances involving Vioxx, the COX-2 inhibitor rofecoxib, illustrate this dilemma. Rofecoxib, a non-steroidal anti-inflammatory drug (NSAID), was developed to treat osteoarthritis, acute pain, and dysmenorrhoea. The drug was heavily marketed and successful in a very short period of time.[245] On September 30, 2004, Merck voluntarily withdrew the drug from the market because of increased risk of cardiovascular disease, mainly myocardial infarction and stroke.[246] FDA and Health Canada approved the drug in May and October of 1999,[247] respectively, despite evidence in pre-

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239 For review, see Eichler *et al.*, *supra* note 94. See also, the discussion of the "trade-off between access and safety" in FDA, "Response", *supra* note 127, and Weiss Smith, *supra* note 182).

240 Health Canada, "Blueprint", and Health Canada, "Concept Paper", *supra* note 23.

241 *Ibid.* at 3.

242 Lemmens & Bouchard, *supra* note 30 at 337; Health Canada, "Concept Paper", *supra* note 23 at 9; Health Canada, "Blueprint", *supra* note 23 at 7.

243 J.B. Ruhl, "Regulation by Adaptive Management—Is it Possible?" (2005) 7 Minnesota Journal of Law Science & Technology 21 at 30, citing Sydney A. Shapiro & Robert L. Glicksman, "The Missing Perspective" (2003) March/April The Environmental Forum at 42 (for comparative pros and cons of "front end" and "back end" policy). See also Bouchard, "Systems" and Bouchard, "Reflections", *supra* note 69.

244 Lemmens & Bouchard, *supra* note 30 at 336. While there is limited power to ensure that manufacturers conduct post-marketing activities, it is noteworthy that s. 23 of the *Food and Drugs Act* regarding the powers of inspectors are very broad. The inspector has the power to do the following: enter into, at any time, a pharmaceutical manufacturing, preparation, preservation or packaging facility (s. 23(1)); examine any pharmaceutical or anything used in its manufacture, preparation, preservation, packaging or storing (s. 23(1)(a)); examine and make copies of any documents/records found in the facility regarding the pharmaceutical (s. 23(1)(c)); and seize and detain any article in relation to which the inspector believes on reasonable grounds that the provisions of the *Food and Drugs Act* or *Regulations* have been contravened (s. 23(1)(d)). These broad powers may be brought into effect in the event that a manufacturer does not comply with its post-marketing obligations. However, even if this is a mechanism by which regulators may enforce post-authorization commitments, it would likely not be used, as "Health Canada has limited tools at its disposal for ensuring continued compliance with the regulations once a drug is on the market": Health Canada, "Concept Paper", *supra* note 23 at 9. Health Canada's "authorities for compliance and enforcement … are outdated, … which limits the range of actions that can be taken, including appropriate sanctions and incentives": Health Canada, "Blueprint", *supra* note 23 at 7.

245 "Vioxx: Lessons for Health Canada and the FDA", Editorial, (2005) 172 Canadian Medical Association Journal 5 [Vioxx, "Lessons"]. See also IMS Health Canada, "New Arthritis Medication Achieves Fastest Adoption Ever Recorded in Canada" *News Release* (2000), online: Longwoods Publishing <http://www.longwoods.com/articles/images/news-Rapid_uptake_new_drugs.pdf> [IMS, "Arthritis"].

246 Barbara Sibbald, "Rofexocib (Vioxx) Voluntarily Withdrawn From the Market" (2004) 171 Canadian Medical Association Journal 1027.

247 U.S., Food and Drug Administration, "Vioxx (Rofecoxib) Questions and Answers: What Did FDA Know About the Risk of Heart Attack and Stroke When it Approved Vioxx?" *Center for Drug Evaluation and Research*, online: FDA

approval clinical trials of a non-statistically significant increase in risk of cardiovascular events.[248] In January 1999,[249] prior to FDA's market approval of Vioxx, Merck launched the Vioxx Gastrointestinal Outcomes Research (VIGOR) study in order to assess side-effects in greater detail.[250] The results of the study, submitted to FDA in June 2000, showed that patients taking Vioxx had fewer stomach ulcers and bleeding than patients taking naproxen, another NSAID; however, the number of serious adverse cardiovascular effects increased.[251] In retrospect, it has been acknowledged that neither agency took into account the fact that these risks might reasonably have been magnified once the drug came into general use,[252] and thus that a need existed for more post-market surveillance. Had more substantial post-market surveillance of safety and efficacy been implemented, it is possible that a significant percentage of serious ADRs could have been reduced, depending on the speed and force of regulatory response.[253] Nevertheless, while three COX-2 selective NSAIDs (celecoxib, rofecoxib, and valdecoxib) have been demonstrated to be associated with increased incidence of serious cardiovascular events,[254] and while Vioxx (rofecoxib) and Bextra (valdecoxib) have been withdrawn for safety reasons, Celebrex (celecoxib) remains on the market.[255]

In its *Blueprint for Renewal*, [256] GOC acknowledges the existing regulatory system is overloaded by tensions emanating from diverse social, economic, scientific, and technological developments such as those enumerated in Table 1, *supra*. Health Canada's goal is to achieve an "adaptable and sustainable regulatory system that: helps Canadians improve their health outcomes through timely access to safe, effective and high-quality health products and food; strengthens safety oversight through a product lifecycle approach; sustains and improves regulatory efficiency and predictability, while maintaining high standards for safety; is accountable, open and transparent to stakeholders and the public; and contributes to better aligned regulatory and reimbursement decision making."[257] The approach is therefore one which recognizes that health products have a lifecycle that encompasses all stages of a drug's development and use.[258]

In a presentation in Ottawa in early 2005,[259] about the time the *Blueprint* was being readied for release to the public, Robert Peterson, then Director General of TPD, used a cartoon to explain why GOC saw the lifecycle approach to be critical—the current regime enshrined in the existing *Food and Drug Act* was seen to be a piano falling from the sky onto an unsuspecting (and it must be said, con-

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<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106290.htm> [FDA, "Vioxx"]; Health Canada, "Vioxx: Notice of Compliance Information", online: Health Canada <http://205.193.93.51/NocWeb/viewnoce.jsp?noc=diif>. See also Health Canada, "Frequently Asked Questions—Vioxx® Recall by Merck: When was Vioxx® approved for use in Canada?" online: Health Canada <http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_50bk2-eng.php>.

248 Vioxx, "Lessons", *supra* note 245.

249 Snigdha Prahash & Vikki Valentine, "Timeline: The Rise and Fall of Vioxx" *National Public Radio*, online: NPR <http://www.npr.org/templates/story/story.php?storyId=5470430>.

250 FDA, "Vioxx", *supra* note 247.

251 *Ibid.*

252 *Ibid.*

253 *Ibid.*; Carpenter *et al.*, *supra* note 78.

254 Memorandum from John K. Jenkins, Paul J. Seligman & Steven Galson, U.S., Food and Drug Administration: Center for Drug Evaluation and Research, "Analysis and Recommendations for Agency Action Regarding Non-Steroidal Anti-Inflammatory Drugs and Cardiovascular Risk" (6 April 2005) online: FDA <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106201.pdf>.

255 With the caveat that the label include a boxed warning highlighting the potential for increased risk of CV events: U.S., Food and Drug Administration: Center for Drug Evaluation and Research, "Cox-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)", online: FDA <http://www.fda.gov/cder/drug/infopage/cox2/>; Health Canada, "Updated Safety Information on Increased Cardiovascular Risk with Celebrex (celecoxib)", online: Health Canada <http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_67-eng.php>. For literature referencing presence (or absence) of adverse CV events due to celecoxib see Nadir Aber *et al.*, "Celecoxib for the Prevention of Colorectal Adenomatous Polyps" (2006) 355 New Eng. J. Med. 885; Monica M. Bertagnolli, "Celecoxib for the Prevention of Sporadic Colorectal Adenomas" (2006) 355 New Eng. J. Med. 873; James M. Brophy, Letter to the Editor, "Cardiovascular Risk Associated with Celecoxib", 352 New Eng. J. Med. 2648.

256 Health Canada, "Blueprint", *supra* note 23 at 1.

257 *Ibid.* at 1-2.

258 *Ibid.* at 3.

259 Peterson, *supra* note 15.

fused looking) person, representing the consuming public. This caricature obviously follows the well described controversies over post-marketing safety whereby the public trusted both their physician and their government to protect them from unsafe drugs. Given these controversies, and their apparent chilling effect on the pharmaceutical industry, the goals of regulatory reform were articulated as follows: facilitating biomedical innovation; creating incentives for drug development when the market itself does not do so; allowing earlier access to new drugs; creating an informed consumer; and increasing the threshold for post-market drug safety. The emphasis on providing incentives to industry to support innovation follows numerous reports from GOC and its consultants over the last number of years on the growing productivity gap in Canada relating to new drug submissions,[260] a trend supported by data in the companion paper.[261] A shift of the balance toward more post-market surveillance was seen to grow naturally out of the scope and depth of injuries suffered from drug controversies of the 1990s and the early years of the following decade, premised on the regulatory observation that traditional pre-market Phase 1-3 clinical trials are powered primarily to assess efficacy rather than safety.[262] By 2005, the question to be answered by global drug regulators was seen as such: Given the bulk of safety information will be gathered predominantly post-market, *when is the right time to release the drug to the public*?

A central component of the answer to this question, debated concomitantly in the U.S.[263] and E.U.[264], is the acceptance, and subsequent reallocation, of uncertainties and risks that are inherent to the entire spectrum of drug development, regulation, and consumption. Based on a growing appreciation of these uncertainties, GOC proposed that there is nothing inventive in acknowledging that safety is not, and indeed cannot, be completely or even strongly quantified at the time of drug approval using current clinical trials best practices.[265] The next logical step is that the "real world" risks of drug consumption be better assessed and addressed in the post-marketing phase.[266]

Other confounding factors were seen to be that Phase 3 studies were too often "fishing expeditions", overly expensive and overly risky for firms, artificial in nature, rarely comparative in nature, commercially oriented rather than therapeutically driven, and highly secretive in nature,[267] all to the detriment of the drug consuming public. Moreover, even when post-marketing obligations were mandated, GOC lacked the jurisdiction to enforce compliance.[268] A lifecycle approach was therefore seen as the preferred vehicle to move products into the marketplace in a probationary manner following "strong Phase 2 clinical trials" under circumstances where GOC "participates in decisions, shares risk and costs in drug development."[269] Risk reallocation does not, however, end there. As noted by Health Canada in its *Real World Drug Safety and Effectiveness* guidance document,[270] successful implementation of the lifecycle approach requires "collaboration of many stakeholders - regulators and policy makers, drug plan managers, health care providers, patients, the pharmaceutical industry, researchers, and private insurers - so that patients experience better health outcomes and fewer adverse events."

According to GOC, a so-called real world drug lifecycle involves all relevant research and development, clinical trial studies, regulatory approval, market authorization, and normative post-market prescribing and use by physicians and the general population.[271] The unique aspect of the lifecycle approach is that there is a continuous accumulation of valuable knowledge about a product that oc-

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260 See the following at *supra* note 158: *ICP Reinventing*, *Guthrie & Munn-Venn*, *EPC Heart*, *TCC Innovate*, and *TCC Five*.
261 Sawicka & Bouchard, *supra* note 60.
262 Peterson, *supra* note 15. For an EU perspective, see Eichler *et al.*, *supra* note 94.
263 *IOM Report*, *supra* note 8.
264 *EMEA CHMP 2* and *EMEA CHMP 3*, *supra* note 12.
265 Eichler *et al.*, *supra* note 94.
266 Peterson, *supra* note 15.
267 *Ibid.*
268 Health Canada, "Blueprint", *supra* note 23.
269 Peterson, *supra* note 15.
270 *Real World Drug Safety*, *supra* note 7.
271 Health Canada, "Blueprint", *supra* note 23 at 16.

curs over its lifecycle, especially with respect to the details of its benefit-risk profile.[272] This progression has obvious ramifications for safety problems arising following market penetration. The tacit assumption is that as a drug's benefit-risk profile changes with time, so too should its approval status[273] as, for example, ADRs not detected during initial clinical trials increase in incidence or severity[274] and drug-drug or other drug interactions become apparent.[275] GOC acknowledges and accepts that the progression in knowledge with the passage of time allows for an opportunity for regulators to adapt to changing conditions over time in order to manage evolving benefit-risk conditions.[276] The lifecycle approach is an example of adaptive,[277] or back-loaded,[278] regulation in that a large percentage of resource allocation is aimed at evaluating drug safety and efficacy following initial market authorization. As discussed in the *Blueprint* and elsewhere,[279] development and rigorous adherence to a kind of "best practices" for (a) physician prescribing, informed by the terms and conditions of market authorizations and (b) ADR reporting by physicians and other health care providers would be critical for success of the regime in the context of real world post-market use given the comparative dearth of pre-market safety (or efficacy) data.

Canada now formally seeks to integrate the lifecycle approach into the nation's drug regulation regime in the form of Bill C-51,[280] which has had its second reading to date. Under the terms of the progressive licensing framework,[281] post-market studies, monitoring, safety surveillance, and risk management plans will be required when a sponsor files its submission.[282] The standard for initial market authorization is a "positive or favourable benefit-risk profile,"[283] with maintenance of market authorization requiring a continuing favourable benefit-risk profile throughout the product's life span.[284] According to Health Canada, this standard requires that, when used as intended by the in-

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272 *Ibid.* at 4.

273 *Ibid.* at 11, 15, 17.

274 *Ibid.* at 14-15.

275 *Ibid.*

276 *Ibid.* at 12.

277 Robert Jervis, *System Effects: Complexity in Political and Social Life* (Princeton, NJ: Princeton University Press 1997); Neil E. Harrison, ed., *Complexity in World Politics: Concepts and Methods of a New Paradigm* (Albany, NY: State University New York Press, 2006); David H. Guston, "Innovation Policy: Not Just Jumbo Shrimp" (2008) 454 Nature 940.

278 Ruhl, *supra* note 243.

279 Peterson, *supra* note 15.

280 *Bill C-51*, *supra* note 10. See also Health Canada, "Concept Paper", *supra* note 23.

281 Health Canada, "Concept Paper", *supra* note 23 at 3.

282 *Ibid.* at 5.

283 The notion of "favourable benefit-risk" is elaborated substantially in the Health Canada, "Concept Paper"*, supra* note 23. At 14, it states that "[a] drug must have a positive benefit-risk profile to be marketed; this means that for the intended use in the intended population the drug's likelihood of causing a benefit outweighs the likelihood of causing a harm. Harm can include treatment failure or an adverse event. Benefits and risks are inherently linked concepts because there are no risks that are acceptable in the absence of benefits". Later (at 19) it states that "the demonstration of efficacy, safety and quality for the proposed conditions of use (e.g. authorised indication, target population, dosing regimen, duration of use)" will be retained as "the baseline requirement for initial market authorisation." And "[i]t will be important, however, to articulate that *safety evidence at time of initial market authorisation would be limited to identifying the most commonly occurring adverse drug reactions*." [*emphasis added*]. At 20, it is underscored that favourable benefit-risk ratio may be required throughout the lifecycle in order to maintain product licensure: "In keeping with the proposed life-cycle approach, maintenance of market authorisation could require a continuing favourable benefit-risk profile for the authorised conditions of use throughout the product's lifespan. The favourable benefit-risk profile would be based on the same elements required for initial market authorisation with some possible additions, i.e., substantial evidence of efficacy, safety, and quality; substantial evidence for a favourable overall benefit-risk profile regarding the product and evidence of other important benefit-risk considerations relating to the impact of market authorisation on external decision-makers." Further context for what constitutes a favourable benefit-risk profile is given at 11, which states that "[a]ll drugs have positive and negative effects. The positive effects, known as benefits, happen when the drug works as intended to prevent, treat, or diagnose an illness. The negative effects, called risks, happen when a drug does not work as intended or it causes an adverse effect. An adverse effect can be a self-limited event like a headache, or a serious life-threatening event such as a heart attack." It could be argued that Health Canada's definition of favourable benefit-risk profile does not take into account the clinical importance of the positive or negative effect. For example, a drug for cancer that causes mild transient nausea in 100% of people would still have a positive benefit-risk profile despite that it only decreases mortality by 2%. Thus, a positive benefit-risk profile would still be found despite that risks, however trivial, outweigh the benefit. This issue would be considered by Health Canada as a "contextual benefit-risk consideration" (i.e. is the drug intended for a serious/debilitating condition?) and the potential benefits of bringing the anti-cancer drug to market may be deemed to outweigh even a high risk of nausea.

284 Health Canada, "Concept Paper", *supra* note 23 at 20.

tended population, the drug's likelihood of causing a benefit or positive effect outweighs the likelihood of causing a harm or negative effect.[285] Benefits occur when a drug works as intended to prevent, treat or diagnose an illness or medical condition.[286] Conversely, risks occur when a drug does not work as intended or if it causes an adverse effect.[287]

Under the lifecycle framework, the benefit-risk assessment for initial market authorization has two broad requirements. The first requirement is scientific evidence of substantial safety, efficacy, and quality for the proposed conditions of use (i.e. authorized indication, target population, dosing regimen, and duration of use) and information that "contextualizes" that evidence (i.e. availability and performance of other therapies, domestic and international clinical practice environments, anticipated use patterns that may lie outside the conditions of use studied in pre-market trials, and anticipated manageability of risks including potential therapeutic impact of remaining uncertainties regarding the drug). The second requirement is information regarding important contextual benefit-risk considerations (i.e. considerations relating to ethics, society, public and/or individual health, and risk acceptance).[288] Maintenance of a market authorization past the initial, or probationary, licensing stage would require a continuing favourable benefit-risk profile throughout the remainder of the drug's lifecycle.[289] The post-market benefit-risk assessment would be based on the same baseline elements as are required for initial market authorization, but with some possible additions[290] such as substantial evidence for a favourable overall benefit-risk profile and evidence of other important benefit-risk considerations relating to the impact of market authorization on external decision makers.[291] Even so, safety evidence at the time of initial market authorization would only be limited to the most commonly occurring adverse drug reactions.[292] The trade-off under PLF is therefore a reduction in the threshold for initial drug approval in exchange for higher monitoring standards post-authorization as a condition for continuing market authorization.[293]

Further allowances for real world use include potential oversight by GOC in the design of post-marketing trials with defined controlled placebo requirements, comparator selection, blinding, and randomization, "structured" release into the market following Phase 2 studies (presumably to reduce risk for the first wave of consumers who will almost certainly have a much greater risk of safety problems than would be the case had Phase 3 studies been performed), determination of data requirements during probationary approval, detailed scrutiny of real-time active data collection, and subsequent modification of labelling as warranted by this data.[294] A critical consideration is that under the terms of Bill C-51, GOC has jurisdiction to attach terms and conditions to an issued licence,[295] including probationary licences, which may include certain field reporting commitments or that further safety and efficacy studies be completed.[296] In this respect, PLF, at least as captured by the provisions of Bill C-51, parallels GOC's existing NOC/*c* policy.

Unlike the general licensing provisions of C.08.004(1) modified by the "conditions of use" under C.08.002(1),[297] Bill C-51 contains specific language directed to licence "terms and conditions". While the provisions of Bill C-51 provide GOC with the desired jurisdiction to grant probationary approval and thus to be more involved in post-market surveillance, they also allow for considerable flexibility on the details and timing of licence issuance, suspension and revocation.[298] Policy grounds for ex-

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285 *Ibid.* at 14.
286 *Ibid.* at 11.
287 *Ibid.*
288 *Ibid.* at 18-20.
289 *Ibid.* at 20.
290 *Ibid.*
291 *Ibid.*
292 *Ibid.* at 19.
293 Paul C. Hébert, "Progressive Licensing Needs Progressive Open Debate" (2007) 176 Canadian Medical Association Journal 1801.
294 Peterson, *supra* note 15.
295 *Bill C-51*, *supra* note 10. See also sections of the Bill enumerated, *supra* notes 20-22.
296 Health Canada, "Concept Paper", *supra* note 23 at 6.
297 See Section I.B above.
298 Specific provisions in *Bill C-51* directed to terms and conditions for clinical trial applications are found in cl. 8 ss.

plicit licence terms are contained in the 2006 *Blueprint*,[299] 2007 Concept Paper,[300] and 2007 amendments to the NOC/*c* policy,[301] all of which focus on the acute need for specific terms and conditions for drugs that qualify for expedited review or flexible departure under conditions where additional safety, efficacy, or effectiveness studies are recommended as a condition of continued marketing authorization.[302] Parallel to the current NOC/*c* policy,[303] there is broad discretion in the provisions of Bill C-51 directed to issuance, revocation, and suspension of market authorizations under conditions where post-marketing safety signals might be accruing rapidly for example, following the first-time exposure of the drug to the general population.[304] This flexibility is linked to the "contextual" benefit-risk mechanism for approval which, despite its "evidence-based" nature,[305] does not provide a guarantee that drugs associated with increasing safety signals will be withdrawn from the market any faster or more efficiently than would take place under the current regime. As acknowledged by regulators elsewhere,[306] this will continue to depend on a semi-quantitative decision-making process that encompasses both objective evidence-based and subjective context-based factors.

2. *Other Jurisdictions*

Canada is not alone in its efforts to legislate PLF and other lifecycle approaches. Indeed, the seeds of the lifecycle model of drug regulation appear to have been sown in an emergent manner[307] in a number of jurisdictions in response to post-marketing safety controversies over the final quarter of the last century.[308] Both FDA[309] and IOM[310] recognized early that drug safety was better served by lifecy-

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18.2(2), 18.2(3) and 18.4(1); for market authorizations in cl. 8 ss. 18.7(2), 18.7(3), 18.7(4), 19.1(b) and 19(1)(1)(b); and for establishment licences in cl. 8 ss. 19.2(2), 19.2(3), 19.2(4), 19.6(1)(b) and 19.7(1)(b).

299 Health Canada, "Blueprint"*, supra* note 23.

300 Health Canada, "Concept Paper", *supra* note 23.

301 *NOC/c Guidance Document*, *supra* note 104.

302 Health Canada, "Concept Paper", *supra* note 23 at 8, 17-19, 26.

303 *NOC/c Guidance Document*, *supra* note 104. For example, under the *NOC/c* policy (at 15, 21, 23, 28), the sponsor is required to submit periodic safety reports semi-annually "until such time as the conditions have been fulfilled and removed." Information provided includes, *inter alia*, commitments regarding enhanced post-market surveillance, including reporting of ADRs and active surveillance responsibilities. We note there are no universal evidence-based rules or standards governing the details of post-market surveillance under the policy, which are to be determined on a "case-by-case basis following discussions between GOC and sponsors." The policy further stipulates that "enhanced post-market surveillance procedures" are mandated for products licensed the NOC/*c* stream, including regular monitoring of the conditions associated with an NOC/*c* and active surveillance. If these enhanced surveillance procedures fail to confirm the safety and efficacy claims made in the original submission, reflected in the relevant conditions of use, the policy stipulates only that "appropriate regulatory action will be taken to ensure the safety of the patients treated." Failure of a sponsor to fulfill the conditions of an NOC/*c* may provide GOC with reason to suspect the product is unsafe or ineffective at that time, with the result that GOC may conclude there is insufficient evidence to establish the effectiveness of the drug for the conditions of use attached to market authorization. For example, under C.01.013 of the *Food and Drug Regulations*, GOC may issue a stop-sale letter or advise that the drug be recalled from the market. The product may however remain available through the SAP or under other conditions authorized under the discretion of the Minister. Whether and how frequently sponsors fulfill conditions attached to NOC/*c* licences is described in detail in the companion article: *Sawicka and Bouchard, supra* note 60, at Fig. 10, Table 5, and discussion thereof.

304 IMS, "Arthritis", *supra* note 245; Carpenter *et al., supra* note 78.

305 Health Canada, "Concept Paper", *supra* note 23 at 5, 19, 20; Health Canada, "Blueprint"*, supra* note 23 at 4, 22; Yeates*, supra* note 23 at 1845-46.

306 *IOM Report*, *supra* note 8; *EMEA CHMP 2* and *EMEA CHMP 3*, *supra* note 12. See also *EMEA Innovation, supra* note 9; *EMEA Road Map*, *supra* note 82.

307 Peter A. Corning, "The Re-Emergence of 'Emergence': A Venerable Concept in Search of a Theory" (2002) 7 Complexity 18 (Emergence refers to the birth of novel structures and institutional functions, including patterns in law and regulation, resulting from the adaptive process of self-organization in complex systems). See also M. Mitchell Waldrop, *Complexity: The Emerging Science at the Edge of Order and Chaos* (New York: Simon & Schuster, 1992).

308 See the following at *supra* note 140: Hilts; Avorn; Krimsky; Angell; and Cohen. See Ray Moynihan & Alan Cassels, *Selling Sickness: How the World's Biggest Pharmaceutical Companies Are Turning Us All Into Patients* (New York: Nation Books, 2005). For a review of the scope of pre-1980 regulatory controversies, see McGarity & Shapiro*, supra* note 192.

309 Food and Drug Administration: Centre for Drug Evaluation, "Concept Paper: Premarketing Risk Assessment (Draft)" (3 March 2003), (on file with author); Federal and Drug Administration: Centre for Drug Evaluation, "Concept Paper: Risk Management Programs (Draft)" (3 March 2003), (on file with author); Food and Drug Administration: Centre for Drug Evaluation "Concept Paper: Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Draft)" (3 March 2003), (on file with author).

cle-based regulatory models, including early articulations of flexible departure and the need to regulate therapeutic products in light of real world drug use. In particular, IOM's *Future of Drug Safety* report is analogous in spirit and precedes the Canadian PLF regime. FDA requested that IOM "convene an ad hoc committee of experts to conduct an independent assessment of the current system for evaluating and ensuring drug safety post-marketing and make recommendations to improve risk assessment, surveillance, and the safe use of drugs."[311] FDA's request was prompted by growing concern over the health risks approved drugs posed to an unsuspecting public.[312]

IOM identified a number of serious problems inherent in FDA's approval process, including a lack of clear regulatory authority, chronic under-funding, organizational difficulties and a scarcity of post-approval data.[313] Psaty and Burke claimed that FDA not only lacks a systematic approach to identifying pre-marketing drug safety issues but is also deficient in following up on recommended post-marketing studies.[314] Indeed a number of independent sources have reported that post-marketing commitments requested by FDA are fulfilled poorly or not at all by pharmaceutical product sponsors once approval has been granted.[315] This situation is enabled by the fact that FDA has no jurisdiction to compel sponsors to complete agreed-upon post-marketing studies or initiate new ones.[316] In fact, the completion rate for these studies has declined from 62% in 1970 to 1984 to only 24% during the period 1998-2003.[317] FDA's current system of post-market surveillance has been strongly criticized in light of its reliance on an ADR reporting system which "collects information on suspected cases and offers only the weakest type of evidence about their association with drug use."[318]

In light of such problems, IOM suggested FDA improve its transparency and credibility through the creation of a culture of safety based on the lifecycle approach to benefit and risk.[319] The committee recommended FDA assure performance of timely and scientifically-valid evaluations, especially where the assessment of benefit-risk continued following market authorization.[320] FDA was mandated to implement an "ongoing systematic effort to monitor safety during the entire market life of a drug,"[321] which in both pith and substance is synonymous with the Canadian PLF regime. IOM further recommended that Congress provide FDA with jurisdiction to mandate post-marketing risk assessment and risk management programs and impose conditions before and after drug approval that reflect the specific safety concerns and benefits presented by the drug.[322] Proposed risk assessment and risk management pro-

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310 Institute of Medicine of the National Academies: Committee on Data Standards for Patient Safety, Board on Health Care Services, "Patient Safety: Achieving a New Standard of Care", online: National Academies Press <http://www.nap.edu/openbook.php?isbn=0309090776> [Board on Health Care Services]. See also Institute of Medicine of the National Academies: Committee on Quality of Health Care in America, "To Err is Human: Building a Safer Health System", online: National Academies Press <http://www.nap.edu/openbook.php?isbn=0309068371> [Committee on Quality of Health Care].

311 *IOM Report*, *supra* note 8 at S-3. See also *FDA Fast Track*, *supra* note 11.

312 *Ibid*. at S-3.

313 Bruce M. Psaty & Sheila P. Burke, "Protecting the Health of the Public—Institute of Medicine Recommendations on Drug Safety" (2006) 355 New Eng. J. Med. 1753 at 1754.

314 *Ibid*. at 1754.

315 *IOM Report, supra* note 8; U.S., Government Accountability Office, *Drug Safety: Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process* (Washington: Government Accountability Office, 2006). See also Jerry Avorn, "Paying for Drug Approvals—Who's Using Whom?" (2007) 356 New Eng. J. Med. 1697; Psaty & Burke, *supra* note 313 at 1754; Psaty & Charo, *supra* note 195 at 1917; Tufts Center, *supra* note 206; U.S., Food and Drug Administration, "Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies" (2005) 70 Federal Register 8379; U.S., Food and Drug Administration, "Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies" (2006) 71 Federal Register 10978; U.S., Food and Drug Administration, "Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies" (2007) 72 Federal Register 5069; Public Citizen, "Study of the Drug Industry's Performance in Finishing Required Postmarketing Research (Phase IV) Studies", HRG Publication #1520 (13 April 2000), online: Public Citizen <http://www.publiccitizen.org/publications/release.cfm?ID=6721> [Public Citizen, "Study"].

316 *IOM Report, supra* note 8. See also Weiss Smith, *supra* note 182; Psaty & Charo, *supra* note 195; Carpenter *et al*., *supra* note 78.

317 Psaty & Charo, *supra* note 195 at 1917. See also Public Citizen, "Study", *supra* note 315.

318 Psaty & Charo, *ibid*.

319 *IOM Report*, *supra* note 8 at S-5.

320 *Ibid*. at S-7.

321 Psaty & Charo, *supra* note 195 at 1917.

322 *IOM Report*, *supra* note 8 at S-11.

grams included the following: (a) compliance with agency-initiated changes in drug labels; (b) specific warnings to be incorporated into all promotional materials; (c) a moratorium on direct-to-consumer advertising; (d) restriction to certain facilities, pharmacists, or physicians with special training or experience; (e) the performance of specified additional clinical trials or other studies; and (f) the maintenance of an active adverse event surveillance system.[323]

In 2007, FDA responded to the IOM.[324] Its response received a mixed review. Some believed the response is consistent with the spirit of IOM report,[325] whereas others claimed it fell far short of what the public deserves in that it demonstrated an overwhelming lack of understanding of the magnitude of the changes recommended by the IOM to create a culture of safety.[326] It was argued that FDA's response offered at best incremental progress, which in and of itself offers a glimpse into the future of drug safety.[327] FDA offered a detailed response to many of the IOM's recommendations (e.g., plans for reviewing the adverse effect reporting system, increasing access to study data from large automated health care databases, evaluating risk minimization plans, developing and systematically improving risk-benefit analyses, creating a new advisory committee on communication with patients and consumers, and developing risk communication plans).[328] Even so, some commentators suggested that the road map offered by FDA appeared to be constrained in certain respects by a lack of resources while other aspects of its response appeared to reflect the culture, visions, and values of an FDA badly in need of change.[329] Indeed, Psaty and Charo[330] and Weiss Smith[331] charge that, when viewed in its entirety, the FDA's response demonstrates its failure to understand the nature of the threats outlined in the IOM Report, namely, those directing FDA to carefully balance public and private interests in drug development: the transparency and independence of the review process; the need to balance pre-approval (access) and post-approval (safety) activities of the agency; and the need to generally keep an arm's length relationship with industry.

On May 9, 2007, the U.S. Senate passed Bill S. 1082, the *Food and Drug Revitalization Act*.[332] In response to the recommendations set out in the IOM report, the Bill enhanced FDA's authority to conduct post-market drug monitoring.[333] On May 22, 2008, shortly after GOC announced Bill C-51, the FDA launched its "Sentinel Initiative" aimed at achieving a national, integrated, and electronic system for monitoring medical product safety.[334] According to FDA, the Sentinel Initiative "will enable FDA to query multiple, existing data sources, such as electronic health record systems and medical claims databases, for information about medical products" and "to query data sources at remote locations, consistent with strong privacy and security safeguards."[335] The ultimate goal of the Sentinel Initiative is to strengthen FDA's ability to monitor medical products throughout their entire lifecycle, consistent with its mandate to enhance the protection and promotion of public health.[336]

The lifecycle approach has also found strong support in the E.U.[337] In a series of detailed and thoughtful reports, EMEA stipulated that "drug development should be considered as a 'continuum' throughout the lifecycle of the product, including post-approval risk management plans with real-life use of the drug" and further that "enhanced post-marketing safety follow-up should be considered to

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323 *Ibid.* at S-9-10.

324 FDA, "Response", *supra* note 127.

325 Galson, *supra* note 76.

326 J.K. Jones, "The Institute of Medicine's Report on Drug Safety: Constructive and Ambitious, But Does it Go Far Enough?" (2007) 81 Clinical Pharmacology & Therapeutics 156; Weiss Smith, *supra* note 182 at 962.

327 Psaty & Charo, *supra* note 195 at 1917, 1919.

328 *Ibid.* at 1917-18.

329 *Ibid.* at 1917, 1919.

330 *Ibid.* at 1919.

331 Weiss Smith, *supra* note 182 at 962. But see Letter to the Editor by Steven K. Galson, former Director of CDER: Galson, *supra* note 76, and Reply to Letter to the Editor by Weiss Smith (2007) 357 New Eng. J. Med. 2521.

332 Bill S. 1082, *Food and Drug Administration Revitalization Act*, 110th Cong., 2007, (not yet referred to a House Committee) online: GovTrack.us <http://www.govtrack.us/congress/bill.xpd?bill=s110-1082>.

333 Hébert, *supra* note 293.

334 FDA, "Sentinel", *supra* note 11.

335 *Ibid.*

336 *Ibid.*

337 For a recent review, see Eichler *et al.*, *supra* note 94.

complement and strengthen the safety during the lifecycle of the product, but could not substitute for what needs to be known before placing the product on the market."[338] EMEA clearly acknowledges the importance of uncertainty and risks of drug development, regulation, and consumption, and the relevance thereof to pre- and post-market safety and efficacy monitoring,[339] conditional marketing authorization, and active post-marketing surveillance.[340] In addition, EMEA clearly recognizes that the danger of expediting approval under conditions of limited information can be balanced to some degree by aggressive post-market surveillance. Allocating resources to both ends of the access-safety balance is seen to provide the benefits of faster approval while mitigating the dangers of marketing a drug too quickly.[341]

II
UPWARDS OR DOWNWARDS ON FOUCAULT'S PENDULUM?

Analogizing concerns over the lifecycle approach to Foucault's pendulum resonates for several reasons. First is the idea of drug development, regulation, and consumption as a constantly moving 360º pendulum that is highly sensitive to *both* its initial starting conditions and to changes in dynamic conditions occurring over time. We can extend this analogy beyond physicist Leon Foucault's work to encompass that of philosopher Michel Foucault, through the convergent nexus of social institutions, power, knowledge, post-structuralism (here, "post" linear regulatory models),[342] and a "thick" moral reading[343] of the diverse motivations of public and private actors making up the rTPL ecology. The exclamation point is Umberto Eco's novel of the same title, with its layers of intricate conspiracies, the likes of which have been invoked almost neurotically as an essential element of drug regulation by many commentators in the last decade. A question at the point of convergence of all these paths might be this: Does the lifecycle approach to drug approval represent a legitimate contextual effort to rebalance pre-market and post-market drug safety, efficacy and effectiveness considerations, or yet a further swing toward the upper reaches of pro-industry regulation?

Given the persistence of concerns relating to post-marketing drug safety,[344] it is perhaps not surprising that a range of criticisms have been leveled at the lifecycle approach despite some of its fairly clear advantages. 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. According to its critics, the result of this scenario is that post-market safety withdrawals will remain significant or even increase in light of flexible departure and that the public will be treated to yet more secondary Me Too and Line Extension products rather than first-of-kind breakthrough therapies.

One of the most contentious aspects of PLF is that it provides GOC with increased "flexibility" to grant faster market authorization for drugs intended for extraordinary circumstances,[345] including those for conditions that are urgent, rare, serious, life-threatening, or where there is an otherwise unmet medical need.[346] PLF allows flexibility in granting initial authorization where promising drugs have a very limited amount of safety and efficacy information available at the time of licensing;[347] for

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338 *EMEA Innovation*, *supra* note 9 at 17-18. See also the following *EMEA CHMP 1*, *EMEA CHMP 2*, and *EMEA CHMP 3*, *supra* note 12; *EMEA Road Map*, *supra* note 82.

339 *EMEA Innovation*, *supra* note 9 at 6.

340 *Ibid.* at 7-8.

341 *Ibid.* at 16.

342 Benoit Godin, "The Linear Model of Innovation: The Historical Construction of an Analytical Framework" (2006) 31 Science, Technology & Human Values 639; Bouchard, "Reflections", *supra* note 69.

343 Michael Walzer, *Thick and Thin: Moral Argument at Home and Abroad* (Notre Dame: University of Notre Dame Press, 1994).

344 For a detailed description of safety and efficacy issues in the period leading up to 1980, see: McGarity & Shapiro, *supra* note 192.

345 See generally *supra* notes 20-21.

346 *Bill C-51*, *supra* note 10 at cl. 8 ss. 18-19. See also Yeates, *supra* note 23 at 1845; Health Canada, "Concept Paper", *supra* note 23 at 10.

347 Health Canada, "Concept Paper", *supra* note 23 at 15.

instance, emergency use drugs that cannot be ethically tested in humans.[348] Health Canada appropriately refers to mechanisms for early approval in face of potentially less safety and efficacy evidence as "flexible departure".[349] However, while the mechanism for increased post-market surveillance has been appropriately lauded, flexible departure has garnered significant criticism given its capacity to depart from the usual evidentiary requirements for safety and efficacy.[350] 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 "contextual" evidence may counterbalance and indeed offset the requirement of substantial safety and efficacy evidence imposed under normal circumstances.[351] Contextual evidence can be evidence showing that potential benefits of marketing the drug will outweigh the relatively increased uncertainty regarding the drug's safety and efficacy.[352]

As discussed *supra*, the terms of flexible departure have been incorporated into Bill C-51, which expressly states 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."[353] However, given the importance of both objective and contextual factors in most emerging lifecycle models of drug regulation,[354] it seems reasonable to speculate that this portion of the Bill is not expressly intended to justify regulatory risk-taking. For example, a "lack of full scientific certainty" could be used to justify withdrawal of a product from the market following a sufficient increase in the frequency of relevant safety signals. This would be consistent with the so-called flexible nature of the proposed regulatory scheme, which presumably would lend itself equally well to both "flexible departure" and "flexible withdrawal."

It is also unknown whether GOC will focus more on Priority Review and NOC/*c*-type approvals once PLF comes into force, thus continuing the post-user fee trend of favouring access over safety. A related issue is a potential reduction in the standard for approval for drugs that depart the pre-approval stage earlier, although federal drug agencies vigorously deny this.[355] Similarly, a shift from the precautionary principle to benefit-risk as the mechanism of flexible departure may conduce to post-market withdrawals, as with earlier observations of shifts in regulatory practices following a change in the political culture underpinning drug approval.[356] Additional concerns have been expressed over whether federal drug agencies will have the required arm's length separation in pre-market and post-market authorization capacity and jurisdiction.[357] A related issue is that GOC may not actually suspend or revoke market authorization once approval has been granted given the increasing partnership between drug regulators and industry over the last two decades.[358] Certainly the multi-stage thresholds for suspension and revocation of clinical trial applications, market authorizations, and establishment licences discussed above allow enormous flexibility and discretion on the part of GOC under the terms of Bill C-51. It would be invaluable in this regard to have data pertaining to historical trends in drug approval by Health Canada as it leads up to its lifecycle approach, particularly data comparing the number of approvals in standard and expedited review streams (Pri-

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348 *Ibid.*

349 *Ibid.* at 21.

350 *Ibid.* at 20-21.

351 *Ibid.* at 21.

352 *Ibid.*

353 *Ibid.* at 20.

354 See generally Section I.C. An additional consideration is that the statement regarding scientific uncertainties is found in the bill's preamble rather than in a specific substantive clause. Typically, a legislative or constitutional preamble is intended to explicate the purpose and underlying philosophy of legislation prior to providing a specific statutory framework, rather than having any real force and effect in law. See *e.g.* Elmer Driedger, *The Composition of Legislation* (Ottawa: The Queen's Printer, 1957) at 93-94.

355 Health Canada, "Blueprint", *supra* note 23; FDA, "Sentinel", *supra* note 11; *EMEA CHMP 2* and *EMEA CHMP 3*, *supra* note 12. See also Eichler *et al.*, *supra* note 94.

356 Abraham & Davis, *supra* note 182; Carpenter *et al.*, *supra* note 78.

357 Weiss Smith, *supra* note 182; Psaty & Charo, *supra* note 195; Eichler *et al.*, *supra* note 94.

358 See generally *NIH Innovation or Stagnation, supra* note 159; Ratner, *supra* note 168; Buckman *et al.*, *supra* note 168; Woosley & Cossman, *supra* note 168; Zerhouni, *supra* note 159; Bernstein, *supra* note 159; FDA, "Response", *supra* note 127; Wiktorowicz, *supra* note 74.

ority Review and NOC/*c*) and in relation to expedited approvals that do (NOC/*c*) and do not (Priority Review) require further evidence of safety to be submitted following initial market authorization.

A growing concern relating to domestic and global drug approval models is the increasing strength and scope of IPR rights associated with therapeutic products. This is a particularly important consideration in light of the increasing privatization of the medical research enterprise and rTPL ecology.[359] A relevant issue is whether the lifecycle approach will continue the trend initiated by NAFTA, TRIPS, and linkage regulations of favouring development of Me Too and Line Extension drugs over development of truly breakthrough products.[360] Data demonstrating trends in the types of drug approvals on which GOC has focused in the lead-up to PLF would be valuable in predicting the types of products to which the public is likely to gain access in a PLF context. Particularly useful would be data relating to the number and per cent of total approvals that were First in Class, Me Too, and Line Extensions, as well as the number and per cent of total approvals that were associated with brand name and generic pharmaceutical firms.

On the other end of a shifting evidentiary balance, the evolution toward lifecycle regulation is clearly motivated by and intended to rectify errors that led to post-marketing safety controversies over the last decade. In this light, GOC deserves credit for pushing the system toward a state of robustness and away from a state where the system was clearly not working.[361] In this light, a critical issue is that this shift in the regulatory approval machinery and leadership are perceived publicly to be occurring in response to calls from industry and apparent patient advocacy groups, under conditions where material information pertaining to drug safety is becoming available exponentially and sometimes for the first time. It is also occurring, however, in response to pleas by Health Canada, and its partner agencies in the U.S. and E.U., to close the gap between the need for enforcement of post-market obligations and agency jurisdiction to do just that. Hence, the idea of dynamic balance in favour of a public health mandate is central to all iterations of the lifecycle approach to drug regulation.[362]

Given the already substantial movement toward faster access in all three jurisdictions, there can be little question that the post-market compliance and enforcement gap is the linchpin for the lifecycle or real world approach to drug regulation. While this gap is set to be remedied by the provisions of Bill C-51 (or future legislation), only the future will reveal how hard a line drug regulators will take when faced with evidence of acute safety problems. As experience with conflicted FDA drug reviewers has shown amply,[363] it will take strongly principled action on the part of agency and government leadership to ensure the delicate balance sought to be effected by PLF is maintained. If put into practice with the teeth the public deserves, PLF and other lifecycle approaches should provide a mechanism to appropriately balance the tangible and intangible costs, benefits and risks of drug development, drug regulation, and drug consumption.[364] If not, it is not inconceivable that we will see even further movement toward post-marketing safety controversies, particularly given GOC's stated goal to move away from traditional Phase 3 studies toward some system of probationary approval follow-

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359 *Ibid.*; Bouchard & Lemmens, "Biomedical", *supra* note 144.

360 Joel Lexchin, "Intellectual Property Rights and the Canadian Pharmaceutical Marketplace: Where Do We Go from Here?" (2005) 35 International Journal of Health Services 237; "Drugs in 2001: A Number of Ruses Unveiled" (2002) 11 Prescrire International 58; Song Hee Hong *et al.*, "Product-Line Extensions and Pricing Strategies of Brand Name Drugs Facing Patent Expiration" (2005) 11 Journal of Managed Care Pharmacy 746; Domenico Motola *et al.*, "An Update on the First Decade of the European Centralized Procedure: How Many Innovative Drugs?" (2006) 62 British Journal of Pharmacology 610. See generally Patented Medicine Prices Review Board, *Annual Report* 2000, online: Patented Medicine Prices Review Board <http://www.pmprb-cepmb.gc.ca/CMFiles/ar00e812NPN-482003-6735.pdf>.

361 Robustness refers to the quality of being able to withstand stresses, pressures, or other changes in environment as a result of the ability to learn and adapt to changing conditions with minimal damage or loss of functionality.

362 For review, see Eichler *et al.*, *supra* note 94.

363 See both Union of Concerned Scientists, and Harris, "Accuse", *supra* note 211.

364 Health Canada, "Blueprint", and Health Canada, "Concept Paper", *supra* note 23; FDA, "Response", *supra* note 127. See also Campbell & Lee, *supra* note 26; McBane, *supra* note 26; Ann Silversides, "Transparency and the Drug Approval Process at Health Canada (2005), online: Women and Health Protection <http://www.whp-apsf.ca/pdf/transparency.pdf>; Graham, "Smart", *supra* note 26.

ing Phase 2 investigations.[365] In light of the self-interest of all other actors in an rTPL ecology, it will be up to government and agency leadership to balance competing interests and protect the public. Details as to the operation of Bill C-51 will wait until the accompanying regulations are tabled and come into force.[366]

III
SUMMARY & CONCLUSIONS

The first part of the article described how the historical drug regulation regime, informed strongly by the Thalidomide crisis of the 1960s, focused on strong pre-market review with little, if any, post-market safety surveillance. The pivot around which the system revolved was a combination of scientific evidence from Phase 1-3 clinical trials and a decision-making matrix that was strongly informed by the relatively risk-averse precautionary principle. A tacit assumption of drug regulation over the last several decades was that, given enough time and resources, regulators could obtain necessary and sufficient evidence regarding a drug's safety and efficacy profile such that that post-marketing problems could be avoided or at least substantially mitigated.

Over time, a host of regulatory subsystems coevolved to affect a substantial increase in the speed of drug review, which in turn resulted in enhanced "access" by the public to newly approved drugs. As reviewed in Section I, these include the institution in all major jurisdictions of user fees, a slow but sure migration from the precautionary principle to risk management principles as the primary basis for regulatory decision making, incentives favouring pharmaceutical innovation revolving around a growing platform of intellectual property and regulatory rights, and a growing number of pathways for expedited approval, some involving market entry before completion of traditional Phase 3 clinical trials.

However, along with enhanced access came a spate of serious and widespread post-marketing drug safety disasters. The sheer persistence and severity of these controversies, including numerous tragedies relating to the morbidity and mortality of children and adolescents due to hiding and otherwise selective reporting of clinical trial data, was mind boggling. This led to widespread public criticism of drug regulators and the means at their disposal to protect the public, if not their intent in doing so. Reports of corporate malfeasance escalated to such an extent that regulators in all major jurisdictions spent substantial resources seeking efficient and effective alternatives to existing drug regulatory regimes. About the same time came a growing recognition by regulators and scholars of the complexity and uncertainties inherent to large scale drug development, regulation and consumption. Thus, was born the lifecycle, or "real world," approach to drug regulation.

Concerns persist, however, as to whether regulatory agencies have the best interests of private firms in mind, or whether lifecycle-based legislation and regulations are truly aimed at rebalancing public and private interests in therapeutic product development. There is no question that Bill C-51 privileges a risk management approach rather than one dominated by the precautionary principle. Moreover, GOC drafted Bill C-51 such that it retains substantial discretion at numerous points in the approval process. This discretion could easily be used to facilitate even more rapid entry of certain drugs into the market despite concerns by regulatory scientists and public commentators with regard to post-marketing safety. Indeed, the legislation provides for highly convoluted multi-stage evidentiary thresholds for suspension and revocation of clinical trial applications, market authorizations and establishment licences. GOC has made it clear that it seeks to replace a system it sees as broken with a system geared toward probationary approval balanced by stronger post-marketing compliance and enforcement measures.

Rebalancing of the regulatory framework is entirely workable in theory. What remains to be seen is whether GOC will bring the same level of tenacity and principled leadership to the post-marketing side of a recalibrated regulatory balance that it has thus far brought to reducing barriers to regula-

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365 Peterson, *supra* note 15.

366 Clause 11 section 30 of *Bill C-51*, *supra* note 10, provides jurisdiction for the Governor in Council to make regulations respecting the operational details of the PLF regime.

tory approval and encouraging innovation via IPR rights. In light of the resources it has put into nurturing, articulating, publicly consulting over, and finally proposing tentative legislation, it would be highly discouraging if more of an effective balance of pre-market and post-market regulatory oversight was not struck when viewed with appropriate hindsight and scale.

Finally, given the pronounced emphasis in developed nations on personal autonomy and choice,[367] and the marketplace as a preferred vector for exercising these rights,[368] it is reasonable to assume that both pharmaceutical firms and the consuming public will continue to act as self-interested and quasi-rational actors more often than not. It therefore falls to government to aggressively referee and balance these interests while serving the goals of making available safe and efficacious products to the public and facilitating innovation in the biomedical sciences in a manner constrained by prevailing legal rights and norms. As acknowledged for some time,[369] it is not knowledge, but action, that lies at the heart of an efficient and effective regulatory regime.

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367 Janice Gross Stein, *The Cult of Efficiency* (Toronto: House of Anansi Press, 2001).

368 Joseph Heath, *The Efficient Society: Why Canada Is As Close To Utopia As It Gets* (Toronto: Penguin, 2001).

369 *IOM Report*, *supra* note 8. See also Board on Health Care Services, *supra* note 310 and Committee on Quality of Health Care, *supra* note 310, citing Goethe to the effect that "Knowing is not enough; we must apply. Willing is not enough; we must do."