EMPIRICAL ANALYSIS OF CANADIAN DRUG APPROVAL DATA 2001-2008: ARE PHARMACEUTICAL PLAYERS "DOING MORE WITH LESS"?

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Canada's proposed new drug regime, termed the "Progressive Licensing Framework" (PLF), has received considerable attention since the announcement of Bill C-51 in 2008. On the one hand, its critics claim that "flexible departure", or expedited approval prior to completion of traditional Phase 3 clinical trials, may lead to a lower standard for drug approval and an increase in unsafe products on the market. Supporters, on the other hand, claim that more emphasis on post-market safety will effectively recalibrate the risks, benefits, and uncertainties of therapeutic product development. We developed a novel empirical model to analyze Canadian drug approval data during the term 2001-2008. Our objectives were to (1) determine the types of candidates that might qualify for flexible departure under PLF and (2) assess the rate and direction of innovative activity by the Canadian pharmaceutical system. The data demonstrate that new drug submissions declined over the test period, whereas follow-on supplementary submissions from both brand name and generic firms increased in a strongly time-dependent manner. New "First in Class" and "Me Too" submissions remained relatively constant over the test period, whereas First in Class and Me Too supplementary submissions increased steeply. Priority reviews, which have the same or similar evidentiary requirements as standard new submissions, declined slightly over the test period, while NOC/c submissions, which have either the same or lower evidentiary requirements as standard submissions with additional post-market obligations, increased steeply. Analysis of withdrawal data reveals that very few substantive NOCs issued over the test period (2,122) were withdrawn to date (0.66%), with no withdrawals for either expedited review stream. Our findings show that concerns expressed over PLF pushing Canada in a new direction with regard to the workings and output of its drug regulatory regime may be misguided in that the existing approval regime has already been anticipating the lifecycle approach for several years. The data also show that the rate and direction of innovative activity by pharmaceutical firms has shifted significantly over time, implying that the domestic pharmaceutical industry, as a whole, is "doing more with less" with existing technologies.

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ABBREVIATIONS[1]

ANDS	Abbreviated New Drug Submission
GOC	Government of Canada
IPR	Intellectual Property & Regulatory
NAS	New Active Substance
NCE	New Chemical Entity
NDS	New Drug Submission
NOC	Notice of Compliance
NOC/*c*	Notice of Compliance with conditions
PLF	Progressive Licensing Framework
R&D	Research and Development
rTPL	regulated Therapeutic Product Lifecycle
S&T	Science and Technology
SNDS	Supplementary New Drug Submission
SANDS	Supplementary Abbreviated New Drug Submission

INTRODUCTION

As discussed in detail in the accompanying article,[2] the Government of Canada (GOC) announced on February 8, 2008 that it would substantially amend the existing *Food and Drugs Act*[3] and *Food and Drug Regulations*[4] to make room for its new "Progressive Licensing Framework" (PLF) for drug approval in the form of Bill C-51.[5] Notwithstanding the nation's state of political upheaval during the time Bill C-51 was tabled, provisions such as those encompassed by Bill C-51 are almost certain to come into force at some point in the near future. This follows the development of a critical mass favouring regulatory reform in Canada, the United States (U.S.), and the European Union (E.U.), spurred in large part by well described post-marketing drug safety controversies. Indeed, Health Canada has invested considerable resources in its lifecycle-based PLF platform over the last several years, which it views as demonstrating global leadership in innovative drug regulation and as a platform for providing strong incentives to pharmaceutical firms to produce innovative products under conditions where the market does not.[6]

A range of concerns have been expressed over newer regulatory models such as PLF that seek to reallocate the risks and benefits of drug development. The concern is that lifecycle models of this nature will in fact yield a lower threshold for initial market authorization, resulting in potentially dangerous drugs slipping through regulatory cracks.[7] Scholars, politicians, public interest groups, and media have argued that recasting drug regulation in this manner will turn the public into "guinea pigs" for drugs that have not been adequately tested,[8] particularly under conditions where post-market studies

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1 The following list comprises abbreviations that are used throughout this article.

2 Ron A. Bouchard & Monika Sawicka, "The Mud and the Blood and the Beer: Canada's New Progressive Licensing Framework for Drug Approval" (2009) 3 McGill J. of L. & Health.

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

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

5 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*].

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

7 Paul C. Hébert, "Progressive Licensing Needs Progressive Open Debate" (2007) 176 Canadian Medical Association Journal 1801; James M. Wright, "Progressive Drug Licensing: An Opportunity to Achieve Transparency and Accountability?" (2007) 176 Canadian Medical Association Journal 1848. See also 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, citing Sir David Cooksey, *A Review of UK Health Research Funding* (London: Her Majesty's Stationary Office, 2006); Ismail Kola & John Landis, "Can the Pharmaceutical Industry Reduce Attrition Rates?" (2004) 3 Nature Reviews Drug Discovery 711.

8 Carly Weeks, "New Drug Rules Pose Grave Risks: Critics" *The Globe and Mail* (8 February 2008) L6 [Weeks, "Critics"].

recommended by regulators are not conducted by sponsors once approval has been given.[9] Fears of this nature are well grounded in light of over two decades of poor decisions by pharmaceutical firms to design, cover-up, or otherwise report clinical trial data selectively.[10] A second important concern relating to PLF and other lifecycle approaches is the linking of flexible approval procedures to a benefit-risk profile that is "favourable" to the drug rather than to the more conservative, and some say more evidence-based, precautionary principle.[11] Canada is not alone in this stance, as parallel criticisms have been voiced over provisions for accelerated[12] and conditional[13] approval in the U.S. and E.U.

The twin arguments by drug agencies in support of the lifecycle approach is that it will help to (1) recalibrate the balance of pre-market and post-market safety and efficacy considerations and (2) stimulate innovation in the pharmaceutical industry, with a concomitant increase in new therapeutic products for the consuming public. In this light, it would be important 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 the standard and expedited review streams (Priority Review and

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9 See generally 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 U.S., Government Accountability Office, *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process* (Washington: Government Accountability Office, 2006); Jerry Avorn, "Paying for Drug Approvals—Who's Using Whom?" (2007) 356 New Eng. J. Med. 1697; 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; Bruce M. Psaty & R. Alta Charo, "FDA Responds to Institute of Medicine Drug Safety Recommendations—In Part" (2007) 297 Journal of the American Medical Association 1917 at 1917; Tufts Center for the Study of Drug Development, "FDA Requested Postmarketing Studies in 73% of Recent New Drug Approvals" (2004) 6:4 Impact Report 1; 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.

10 Craig J. Whittington *et al.*, "Selective Serotonin Reuptake Inhibitors in Childhood Depression: Systematic Review of Published versus Unpublished Data" (2004) 363 Lancet 1341; Jeffrey R. Lisse *et al.*, "Gastrointestinal Tolerability and Effectiveness of Rofecoxib versus Naproxen in the Treatment of Osteoarthritis: A Randomized, Controlled Trial" (2003) 139 Annals of Internal Medicine 539; Gregory D. Curfman, Stepen Morrissey & Jeffrey M. Drazen, "Expression of Concern: Bombardier *et al.*, 'Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis'" (2005) 353 New Eng. J. Med. 2813; Gregory D. Curfman, Stephen Morrissey & Jeffrey M. Drazen, "Expression of Concern Reaffirmed" (2006) 354 New Eng. J. Med. 1193; Bruce M. Psaty *et al.*, "Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis" (2004) 292 Journal of the American Medical Association 2622; Bruce M. Psaty & Curt D. Furberg, "COX-2 Inhibitors: Lessons in Drug Safety" (2005) 352 New Eng. J. Med. 1133; Bruce M. Psaty & Noel S. Weiss, "NSAID Trials and the Choice of Comparators: Questions of Public Health Importance" (2007) 356 New Eng. J. Med. 328; Bruce M. Psaty, Noel S. Weiss & Curt D. Furberg, "Recent Trials in Hypertension: Compelling Science or Commercial Speech?" (2006) 295 Journal of the American Medical Association 1704.

11 Sheila Weiss Smith, "Reply to Galson" (2007) 357 New Eng. J. Med. 2521 [Weiss Smith, "Reply to Galson"] (elaborates on this approach (at 2521), stating that drug-approval decisions are based on a relatively narrow "evidence-based" interpretation of benefit-risk: "Benefits are defined according to the intended effect and intended population, as proposed by the sponsor. These factors are measured in efficacy studies performed in a modest number of carefully selected patients, who may or may not reflect the characteristics of the broader population likely to receive the drug. Furthermore, benefits may be extrapolated from surrogate markers … " and "[t]he approval question becomes 'are there persons for whom the potential benefits could outweigh the known risks?' This standard is reasonable in limited circumstances, particularly for drugs for imminently fatal conditions … otherwise, such a narrow interpretation of risks and benefits, which tends to favour industry over public health, has resulted in many of the FDA's most prominent failures"). See also Sheila Weiss Smith, "Sidelining Safety—The FDA's Inadequate Response to the IOM" (2007) 357 New Eng. J. Med. 960 [Weiss Smith, "Sidelining"]; Steven K. Galson, "The FDA and the IOM Report", Note to Editor (2007) 357 New Eng. J. Med. 2520.

12 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: U.S. Department of Health & Human Services <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm> [FDA, "Fast Track"].

13 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" (London: European Medicines Agency, 2006) online: EMEA <http://www.emea.europa.eu/pdfs/human/regaffair/50995106en.pdf> [EMEA, "CHMP Guideline"].

Notice of Compliance with conditions, or NOC/*c*) as well as expedited approvals that do (NOC/*c*) and do not (Priority Review) require further evidence of safety to be submitted following initial market authorization. In addition, data demonstrating trends in the types of drug approvals issued in the lead-up to PLF would be invaluable in predicting the types of products to which the public is likely to gain access in a post-PLF context. Particularly useful would be data relating to the number and percent of total approvals that were "First in Class", "Me Too", and "Line Extensions,"[14] as well as those granted to brand name and generic pharmaceutical firms. Data of this nature would help clarify the influence of drug regulation on the rate and direction of innovative activity by the domestic pharmaceutical industry.

Considerations such as those expressed above led to the current study. One of our goals was to develop an independent empirical methodology and synthetic model to investigate what types of drug candidates might qualify for flexible departure under Bill C-51 or related PLF legislation and assess the post-market fate of these candidates. A second and related goal was to use this model to identify patterns in the rate (how much) and direction (what kind) of innovative activity by Canadian brand name and generic pharmaceutical firms and analyze this data in relation to GOC's proposed policy goals respecting lifecycle regulation. We empirically analyzed 2,122 substantive Notices of Compliance (NOCs) granted by GOC during the period 2001-2008 to assess meta-trends in the pattern of drug approvals, particularly with regard to submissions for "new" drugs and how these compared with data on "supplemental" Me Too and Line Extension submissions using classifications provided by Health Canada. We found that GOC is already approving drugs with PLF in mind, that there is a significant and potentially growing proportion of drugs entering the market with evidence of safety still required to be met through post-marketing studies, and that very few of the drugs approved during the period of analysis, including those via the two expedited streams, have been withdrawn to date. The data also speak to the strength of the functional relationship between two supposed independent "silos" in a regulated Therapeutic Product Lifecycle (rTPL) innovation ecology[15] e.g., drug regulation and the national science and technology (S&T) polices designed to enhance domestic competitiveness via intellectual property and regulatory (IPR) rights. We conclude that PLF has already been incorporated into the nation's drug regulation framework and that the domestic pharmaceutical industry, as a whole, is focused more on leveraging and extending the value of existing technologies and IPR rights rather than on the production of novel first-of-kind "breakthrough" technologies.

I
ANALYSIS

A. General

On its website, Health Canada posts a listing[16] of all drugs that have received an NOC since 1991. The listing is divided by year and according to the following headings: Biologic products for human use; Non-prescription products for human use; Products for veterinary use, and Prescription products for human use.

Biologics[17] are defined as "drug products derived from biological sources that are listed on Schedule D of the *Food and Drugs Act*. The list includes blood products, cells and tissues, gene therapies, vaccines, radiopharmaceuticals, and therapeutic products derived through biotechnology."[18] Schedule

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[14] Working definitions are provided in Section I.B for "First in Class," "Me Too," "Line Extension", and "New Active Substance".

[15] For discussion of innovation ecology in the basic and medical sciences, see William A. 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" (2008) 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"].

[16] Health Canada, "Drugs and Health Products—Notice of Compliance Listings", online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/list/index-eng.php>.

[17] Health Canada, "Biologics, Radiopharmaceuticals and Genetic Therapies", online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index-eng.php>.

[18] Eileen McMahon & Teresa A. Reguly, "Canada: Follow-on Biologics in Canada" (2008) 3 Update 43 at 43, online: Mondaq: Pharmaceutical, Healthcare & Life Sciences <http://www.mondaq.com/article.asp?articleid=61359>.

D also includes: allergenic substances used for the treatment or diagnosis of allergic or immunological diseases; drugs obtained by recombinant DNA procedures; drugs other than antibiotics prepared from micro-organisms; monoclonal antibodies, their conjugates, and derivatives; snake venom; and other products.[19] Non-prescription products include over-the-counter medications[20] and natural health products such as vitamins, minerals, and herbal remedies.[21] Products for veterinary use, as the name suggests, are those therapeutic products intended for use in animals. Prescription products for human use include those products that contain as medicinal ingredients any of the compounds listed in Part I and II of Schedule F of the *Food and Drug Regulations*. The remainder of the paper will be directed at pharmaceutical products for human use.

NOCs can be granted in an "expedited" fashion in one of two ways.[22] One is through Priority Review,[23] which refers to 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 wherein there exists an unmet medical need or for which a substantial improvement in the benefit-risk profile of the therapy is demonstrated.[24] Evidentiary requirements for safety, efficacy, and quality parallel those for non-priority submissions; the main difference being an accelerated review time.[25] In addition to Priority Review, sponsors may also be granted an NOC with conditions (NOC/*c*)[26] for eligible NDS or SNDS submissions directed to serious, life-threatening, or severely debilitating diseases or conditions for which there is promising evidence of clinical effectiveness based on available data.[27] In addition to less onerous evidentiary requirements, the review process for NOC/*c* approval is significantly accelerated.[28] The main difference compared to Priority Review is that licensure is granted on the "condition" that the sponsor perform additional studies to confirm the drug's alleged therapeutic benefit. Even so, GOC has nominal jurisdiction to ensure a manufacturer's compliance through post-market surveillance.[29] Table 1 shows examples of NOC/*c* approvals recently granted by GOC.

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[19] *Food and Drugs Act*, *supra* note 3 at Sch. D.

[20] For a listing of non-prescription pharmaceuticals given a Notice of Compliance from 1991 to the present date see Health Canada, "Drugs and Health Products—Notice of Compliance Listings", online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/list/index-eng.php#2008>.

[21] For a comprehensive description of natural health products see Health Canada, "Drugs and Health Products—Natural Health Products", online: <http://www.hc-sc.gc.ca/dhp-mps/prodnatur/index-eng.php>.

[22] For a detailed discussion of expedited review pathways in Canada, see Bouchard & Sawicka, *supra* note 2 at Section I.B.

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

[24] *Ibid*. at 1-2.

[25] Trudo Lemmens & Ron A. Bouchard, "Regulation of Pharmaceuticals in Canada" in Jocelyn Downie, Timothy Caulfield & Colleen Flood, eds., *Canadian Health Law and Policy*, 3rd ed. (Toronto: LexisNexis, 2007) 311 at 328; Health Canada, "Priority Review Guidance Document", *supra* note 23.

[26] 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), and C.05.006(2)(a).

[27] Health Canada, *Guidance for Industry: Notice of Compliance with conditions* (Ottawa: Public Works and Government Services Canada, 2007), online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/noccg_accd-eng.pdf>. A candidate for NOC/*c* must have the potential to provide an 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, preventative or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada.

[28] Health Canada, "Access to Therapeutic Products: The Regulatory Process in Canada—Target Review Times", online: Health Canada <http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/access-therapeutic_acces-therapeutique-eng.php#6.2>.

[29] Lemmens & Bouchard, *supra* note 25 at 329.

TABLE 1. EXAMPLES OF RECENTLY ISSUED NOC/*c* APPROVALS

NOC/*c*	Active Ingredent	Date	Indication	Significance	Priority	NAS
Isentress®	Raltegravir Potassium	2007-11-27	HIV integrase strand transfer inhibitor	HIV/AIDS	YES	YES
Duodopa®	Levodopa Carbidopa monohydrate	2007-03-01	Parkinson's	Parkinson's Disease	NO	NO
Lyrica®	Pregabalin	2007-11-09	Analgesic	Neuropathic pain	NO	NO
Atriance®	Nelarabine	2007-09-22	Anti-neoplastic	Adult & child T-cell acute lymphoblastic leukemia/T-cell lymphoblastic lymphoma	NO	YES

A statistical analysis of NOCs issued in Canada from January 1st 2001 to December 31st 2008 inclusive was conducted. For each year, Health Canada's "Prescription Products for Human Use" NOC listing (listing) was analyzed. A listing for a given year encompasses NOCs issued from January 1st of that year to December 31st. With respect to each NOC issued, the listing provides the following information: (a) the brand name of the prescription product that received the NOC; (b) the source of the prescription product (i.e. manufacturer or company name); (c) the active ingredient of the prescription product; (d) the date the NOC was granted; (e) the drug identification number (DIN) assigned to the prescription product upon granting of the NOC; (f) the therapeutic class of that product (i.e. the specific indication or condition for which that prescription product is intended to be used); and (g) any additional comments such as the dosage requirement, route of administration, and whether the NOC was granted due to the manufacturer and/or product's name change among other things. The listing explicitly states whether an NOC was issued under the NOC/*c* policy. Figure 1 illustrates how an NOC is presented in the listing.

Brand Name:	Cialis
Source:	Eli Lilly Canada Inc.
Active Ingredient:	Tadalafil
Comments:	Manufacturer name change; TAB (2.5mg, 5mg, 10mg, 20 mg) ORL
Date:	2007-09-11
DIN:	0229688, 02296896, 02248088, 02248089
Therapeutic Class:	cGMP-Specific Phosphodiesterase Type 5 Inhibitor / Treatment of Erectile Dysfunction
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Brand Name:	Isentress ISSUED UNDER THE NOC/C POLICY
Source:	Merck Frosst Canada Ltd., Merck Frosst Canada Ltée
Active Ingredient:	Raltegravir (supplied as Raltegravir potassium)
Comments:	TAB (400mg)ORL
Date:	2007-11-27
DIN:	02301881
Therapeutic Class:	HIV integrase strand transfer inhibitor

Fig. 1 Example of two entries as they appear in the Health Canada NOC listing

Health Canada's NOC listing has some notable limitations. First, although it is organized alphabetically, listed drugs are not numbered. Therefore, calculating the total number of NOCs issued in a particular year must be done manually. Second, the listing does not specify certain relevant information such as (a) whether an NOC for a given prescription product was issued under New Drug Submission (NDS), Supplementary New Drug Submission (SNDS), Abbreviated New Drug Submission (ANDS), or Supplementary Abbreviated New Drug Submission (SANDS) application stream(s), (b)

whether an NOC was granted under the Priority Review policy, and (c) whether a given prescription product contains a New Active Substance (NAS). Previously known as a "New Chemical Entity" (NCE), an NAS may be directed to the following: a chemical or biological substance not previously approved for sale in Canada as a drug; an isomer, derivative, or salt of a chemical substance previously approved for sale as a drug in Canada but differing in properties with regard to safety and efficacy; or a biological substance previously approved for sale in Canada as a drug, but differing in molecular structure, nature of the source material or manufacturing process.[30] Initially, we deemed drugs classified as NAS as "First in Class". However, Health Canada clarified that NAS drugs are not always first in their class, although on some occasions they can be.[31] The definition of an NAS therefore determines both First in Class and Me Too compound-indication classifications (cf. Table 2).

Health Canada has supplemented the listings with a searchable database (database) that includes all NOCs issued in Canada since 1994. The database can be searched by a product's brand name, drug identification number (DIN), NOC/*c* status, medicinal ingredient, manufacturer, submission class (NAS, Priority, Priority-NAS, or Other), therapeutic class, and type (veterinary, non-prescription, prescription, biologic, or radiopharmaceutical).

To obtain additional information for our listings for each given year, we searched the database by product type (prescription pharmaceutical) and NOC date. Because entering a full year in the date field yielded too many NOCs to hold on one page, each year was broken up into three portions. For example, 2007 was subdivided into January 1 - April 30, May 1 - August 31, and September 1 - December 31. This method generated three NOC lists for a given year, identifying drug brand name, manufacturer, NOC date, medicinal ingredient(s) and DIN. The lists are arranged by date (from most to least recent NOC) and numbered. Numbering allows for easy calculation of the total NOCs in the list. Figure 2 illustrates the beginning portion of the database-generated list for January 1, 2007 to April 30, 2007.

1. HYOSCINE BUTYLBROMIDE INJECTION SANDOZ STANDARD
Manufacturer: SANDOZ CANADA INCORPORATED
NOC Date: 2007-04-27
Medicinal Ingredients: HYOSCINE BUTYLBROMIDE
DIN: 02229868

2. ATRIDOX
Manufacturer: TOLMAR INC
NOC Date: 2007-04-27
Medicinal Ingredients: DOXYCYCLINE HYCLATE
DIN: 02242473

3. PMS-TERBINAFINE
Manufacturer: PHARMASCIENCE INC.
NOC Date: 2007-04-26
Medicinal Ingredients: TERBINAFINE HCL
DIN: 02294273

4. RATIO-TAMSULOSIN
Manufacturer: RATIOPHARM INC.
NOC Date: 2007-04-26
Medicinal Ingredients: TAMSULOSIN HYDROCHLORIDE
DIN: 02294265

[30] Health Canada, "Drugs and Health Products—New Active Substance" (4 June 1991), online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/nas_nsa_pol-eng.php> [Health Canada, "NAS"]; Health Canada, "Drugs and Health Products—NOC Database Terminology" (1 October 2004), online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/noc-acc/term_noc_acc-eng.php>.

[31] Personal communications with David K. Lee (Director, Progressive Licensing Project, TPD, 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) (April-July 2008), [Health Canada Personal Communication]. One of us (Bouchard) also participated in Health Canada's PLF stakeholder workshops in November 2006, May 2007, and June 2007.

Fig. 2 Example of Health Canada NOC database-generated list for January 1, 2007 to April 30, 2007. Entries shown are the first four in the database-generated list.

Within the database-generated list, the drug name (shown in bold and underlined capital letters) can be isolated to obtain "Notice of Compliance Information" for a given drug. The NOC Information page provides a product's NOC date, manufacturer name, type, NOC/*c* status, submission type (NDS, SNDS, ANDS, or SANDS), reason for supplement if the submission is an SNDS or SANDS (i.e. change in dosage, form, or route of administration), submission class (NAS, Priority, Priority-NAS, or Other), therapeutic class, Canadian reference product if the product is a generic, company name, and country of manufacture. Furthermore, the NOC Information provides the product's DIN, medicinal ingredient(s), form, route of administration, and dosage. Figure 3 illustrates the Notice of Compliance Information sheet for the first drug shown in Fig. 2, Hyoscine Butylbromide Injection Sandoz Standard.

Notice of Compliance Information

NOC Date:	2007-04-27
Manufacturer:	SANDOZ CANADA INCORPORATED
Product Type:	PRESCRIPTION PHARMACEUTICAL
NOC with conditions:	No
Submission type:	ANDS
Submission class:	OTHER
Therapeutic class:	ANTISPASMODIC
Canadian Reference Product:	BUSCOPAN
Company:	BOEHRINGER INGELHEIM
Country:	CANADA

Brand 1 of 1:
HYOSCINE BUTYLBROMIDE INJECTION SANDOZ STANDARD

Product 1 of 1:
DIN: 02229868
Form: SOLUTION
Routes: INTRAMUSCULAR, SUBCUTANEUS, INTRAVENOUS

Medicinal Ingredients:

Ingredient	Strength
HYOSCINE BUTYLBROMIDE	20 MG/ML

Fig. 3 Example of a Notice of Compliance Information Sheet as it appears on the Health Canada NOC database. The sheet was obtained by selecting the first drug in the database-generated list shown in Fig. 2.

For each pharmaceutical in the NOC listing, we included additional information found exclusively in the NOC Information through the database-generated list. NOC Information for a given drug in the listing is also available by simply typing in a particular product's brand name and NOC date, which bypasses the database-generated list. This method, although equally effective and accurate, is painstaking as it takes a considerable amount of time to type in the drug name and NOC date and wait for the database to bring up the desired result. Therefore, a database-generated list for the year, albeit broken up into three portions, was the preferred method of proceeding with the analysis.

B. Methods

Each drug within each year's (2001 to 2008) listing was classified as an NDS, SNDS, ANDS, or SANDS based on the NOC Information sheet. The total numbers of NDS, SNDS, ANDS, and SANDS were calculated for each year and then double checked by a blind party for accuracy. Unfortunately, the database is not searchable by submission class (i.e. NDS, SNDS, ANDS, and SNDS). For example, we could not search the database by SANDS and year to get a complete list of all prescription pharmaceuticals that received an NOC by virtue of a SANDS application for that year. This is a significant limitation of the Health Canada database.

Initially, we counted all NOCs issued as NDSs. However, a sponsor may manufacture a drug and receive an NOC by virtue of NDS even if the drug does not differ in any respect (i.e. indication, medicinal ingredient, route of administration, or dosage) from a previous drug manufactured by that company. Health Canada mandates that where there is a change in the manufacturer and/or product name or manufacturing site, a drug manufacturer must apply for a new NOC by virtue of an NDS for any drug issued after such a change took place, even if the drug is not new in any other way.[32] These NDSs are collectively termed by Health Canada as "administrative NDSs."[33] Given these NDSs exist solely because of a product or manufacturer change and not because a new drug was issued an NOC, the presence of these NOCs contaminated the data. Therefore, all administrative NDSs were excised prior to analysis. Administrative ANDS NOCs were excised for the same reason. In order to determine which NOCs were administrative, comments provided in the listing were reviewed. The comments clearly stated whether an NOC was granted by virtue of a simple manufacturer or product name change. Once these NOCs were identified, they were subtracted from the initial total number of NDS and ANDS NOCs to yield an accurate representation of how many substantive NDS and ANDS NOCs were issued in a given year.

The percentage of total NDSs in a given year was calculated in two ways. The first involved the inclusion of generic drugs; therefore, the percentage of NDS was calculated as a fraction of the combined total for all NDS, SNDS, ANDS, and SANDS for that respective year. This is summarized by Equation 1:

$$\% \text{ NDS} = \text{NDS} / (\text{NDS}+\text{SNDS}+\text{ANDS}+\text{SANDS}) \qquad \textit{Eq. 1}$$

The second method involved the exclusion of generic drugs; therefore, the percentage of NDS was calculated as a fraction of the combined total for all NDS and SNDS for that respective year. This is given by Equation 2:

$$\% \text{ NDS} = \text{NDS} / (\text{NDS}+\text{SNDS}) \qquad \textit{Eq. 2}$$

The percentage of SNDSs in a given year was calculated in the same two ways as NDSs. In the first method the percent SNDS was calculated as a fraction of the combined total for all NDS, SNDS, ANDS, and SANDS for that respective year. This is summarized by Equation 3:

$$\% \text{ SNDS} = \text{SNDS} / (\text{NDS}+\text{SNDS}+\text{ANDS}+\text{SANDS}) \qquad \textit{Eq. 3}$$

In the second method, the percentage of SNDS was calculated as a fraction of the combined total for all NDS and SNDS for that respective year. This is summarized as follows:

$$\% \text{ SNDS} = \text{SNDS} / (\text{NDS}+\text{SNDS}) \qquad \textit{Eq. 4}$$

The total number of NOCs classified as NAS was calculated for each year, 2001 to 2008 inclusive. The Health Canada database is searchable by Submission Class, which includes the following categories: NAS, Priority, Priority-NAS, and Other status. By narrowing the search to prescription pharmaceuticals, a specified year, and NAS, we obtained a numerated list of all NOCs with NAS status that were issued in each given year. Subsequently, we narrowed the search to prescription pharmaceuticals, a specified year and Priority-NAS and obtained a numerated list of all NOCs with Priority-NAS status issued in that year. To calculate the total number of NOCs classified as NAS, we added the totals of both NAS and Priority-NAS NOCs. This is summarized by Equation 5:

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[32] Health Canada Personal Communication, *supra* note 31.

[33] *Ibid.*

$$\text{Total NAS} = \text{NAS} + \text{Priority-NAS} \qquad \textit{Eq. 5}$$

Prescription pharmaceuticals classified as NAS are only submitted as NDS. However, for the sake of consistency, the percentage of NAS NOCs was also calculated as a fraction of the combined total of NDS and SNDS (ANDS and SANDS were excluded). This is summarized by Equation 6:

$$\%\ \text{NAS} = \text{NAS} / (\text{NDS}+\text{SNDS}) \qquad \textit{Eq. 6}$$

The percentage of ANDS in a given year was calculated as a fraction of the combined total for all NDS, SNDS, ANDS, and SANDS for that respective year:

$$\%\ \text{ANDS} = \text{ANDS} / (\text{NDS}+\text{SNDS}+\text{ANDS}+\text{SANDS}) \qquad \textit{Eq. 7}$$

The percentage of SANDS in a given year was calculated as a fraction of the combined total for all NDS, SNDS, ANDS, and SANDS for that respective year:

$$\%\ \text{SANDS} = \text{SANDS} / (\text{NDS}+\text{SNDS}+\text{ANDS}+\text{SANDS}) \qquad \textit{Eq. 8}$$

The next part of the analysis involved determination of NOCs classified as First in Class or Me Too. This proved to be one of the most difficult aspects of the study, as available definitions of First in Class and Me Too by regulators are very limited. We used information obtained directly from Health Canada to define First in Class and Me Too drugs. We then designed a methodology for determining which NOCs fall under these categories. This methodology is based on the principles outlined below.

According to Health Canada, "First in Class" drugs are drugs that consist of either (a) a new family of active ingredient(s) or (b) old active ingredient(s) used for the treatment of a new indication (Table 2). Therefore, a drug is deemed to be First in Class if there is no other drug on the market that belongs to the same compound family and is used for the same indication.[34] In other words, a First in Class drug is a drug for which there is no comparator.[35]

Conversely, "Me Too" drugs are drugs that offer important therapeutic options with little or no change to the benefit-risk profile.[36] They are drugs that are comparable to others in terms of their compound and indication.[37] Derivatives or salts of an existing compound are classified as Me Too drugs.[38] As per the Health Canada definition, NAS NOCs include those directed to salts and derivatives.[39] Therefore, drugs that are labeled as an "NAS" can be either First in Class or Me Too drugs. Initially, we assumed Me Too drugs could only be submitted as NDSs. The reasoning for this was that Me Too drugs are neither generic drugs (ANDS or SANDS) nor Line Extensions (SNDS). However, as shown in Table 2, neither First in Class nor Me Too classifications stop at NOCs submitted as NDSs, depending on the chemical nature and use of the compound. SNDS NOCs can be classified as First in Class or Me Too; thus both can be issued as NDS and Line Extension (SNDS) NOCs.[40]

Based on the drug classification scheme outlined in Table 2, we determined which NDS and SNDS NOCs were First in Class and Me Too drugs. We analyzed all NOCs submitted as NDS for approval first. In analyzing this group, we started off with those NDSs deemed by Health Canada to have NAS status, as all First in Class drugs would be included in this broad group. Obtaining a list of all NAS

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34 *Ibid.*
35 *Ibid.*
36 *Ibid.*
37 *Ibid.*
38 *Ibid.*
39 Health Canada, "NAS", *supra* note 30.
40 Health Canada Personal Communication, *supra* note 31.

NOCs for a given year is relatively straightforward, given the ability to search the NOC database by NAS status.

TABLE 2. HEALTH CANADA COMPOUND-INDICATION CLASSIFICATION

YEAR	COMPOUND/INDICATION	CLASSIFICATION
2000	Compound X (first 'X' Compound) with Indication A	First in Class
2001	Compound X with Indication B	First in Class
2001	Compound *a*X (Compound in the family of X) with Indication A	Me Too
2001	Compound *a*X with Indication B	Me Too
2001	Compound *a*X with Indication C	First in Class

We assessed each NAS for the period 2001-2008 by cross-referencing the NAS drug's active ingredient, NOC date, and indication with the Health Canada online NOC database and the World Health Organization (WHO) Collaborating Center for Drug Statistics Methodology website.[41] If the active ingredient in the NAS was the very first of its family of compounds, the drug was classified as First in Class. If the active ingredient in the NAS was a member of a family of compounds in which a drug already exists but the drug was used for a new indication, the drug was also classified as a First in Class. All NAS not deemed to be First in Class were labeled Me Too NOCs. The number of First in Class NDS NOCs was then calculated. The total number of Me Too NDS NOCs for each year was calculated using Equation 9:

$$\text{Total NDS Me Too} = \text{NDS} - \text{First in Class NDS} \qquad \textit{Eq. 9}$$

We then analyzed all NOCs submitted as SNDS. Because SNDS drugs are "Line Extensions" of previously existing drugs, the analysis turned strictly on new indications. Essentially, if an SNDS for a particular compound was given a new indication not seen before, as determined by cross-referencing the drug's active ingredient, NOC date, and indication with the NOC database, it was deemed as a First in Class drug.

The designation of First in Class by virtue of a new indication was far from simple. The starting point for this process was the NAS. If Health Canada classified an NOC as being directed to an NAS, it can be assumed that the active ingredient has not been sold in Canada for that specific indication prior to issuance of the NOC. The next step was to determine whether a new indication exists for the medicinal ingredient associated with the NAS following issuance. One way to do this is via Health Canada's searchable database. We entered the medicinal ingredient described by the NAS into the appropriate database field. This yielded a list of all drugs that have the same medicinal ingredient as the NAS. Because the list is arranged by date, the NAS presents as the earliest entry in the list. The next step was to go through each drug listed above the NAS and determine whether it is an SNDS with a new indication, which is indicative of a First in Class drug. Given that the database only goes as far back as 1994, this method may not produce the most accurate quantification. Part of the difficulty in correctly determining First in Class NOCs is that the NOC database includes, when describing reasons for SNDS (as opposed to NDS), NOCs directed to new indications as well as new routes of administration, dosage forms, and contra-indications.[42] Thus, within the new indication SNDS category, an NOC can be given for a new medical condition as well as for an extended treatment population e.g., pediatric. However,

[41] Online: World Health Organization Collaborating Centre for Drug Statistics Methodology <http://www.whocc.no/atcddd/> [WHO Website].

[42] *Food and Drug Regulations*, *supra* note 4 at s. C.08.003(2).

only NOCs directed to new medical conditions are viewed by Health Canada as First in Class.[43] Therefore, assuming that all NOCs in the extended population SNDS subclass are First in Class would artificially increase the number of true First in Class NOCs. All SNDS NOCs not deemed First in Class were labeled Me Too by default.[44]

The number of First in Class SNDS drugs was calculated as described above. The total number of SNDS Me Too drugs for each year is calculated using equation 10:

$$\text{Total SNDS Me Too} = \text{SNDS} - \text{First in Class SNDS} \qquad \textit{Eq. 10}$$

The next step was to calculate the total number of NOC/*c* during the period 2001-2008. By narrowing search terms on the Health Canada database to prescription pharmaceuticals, a specific year, and NOC/*c*, we obtained a list of all NOC/*c* that were issued in a given year. Because prescription pharmaceuticals provided with market authorization under the NOC/*c* policy are only submitted as NDS or SNDS, the percentage of NOC/*c* was calculated as the fraction of total of NDS and SNDS (e.g., ANDS and SANDS were excluded). This is summarized by Equation 11:

$$\%\ \text{NOC}/c = \text{NOC}/c\ /\ (\text{NDS}+\text{SNDS}) \qquad \textit{Eq. 11}$$

The total number of NOCs issued under Priority Review was calculated for 2001-2008 inclusive. By narrowing the database search to prescription pharmaceuticals, a specific year and Priority Review, we obtained a numerated list of all NOCs issued under Priority Review for that given year. We then searched the database by prescription pharmaceuticals, a specific year and Priority-NAS status and obtained a numerated list of all NOCs with NAS status and that were issued under the Priority Review Policy in that given year. To calculate the total number of NOCs granted via the Priority Review stream we added the totals of both Priority and Priority-NAS NOCs as given by Equation 12:

$$\text{Total Priority} = \text{Priority} + \text{Priority-NAS} \qquad \textit{Eq. 12}$$

Prescription pharmaceuticals granted an NOC under the Priority Review Policy are only submitted for approval as NDS or SNDS. Thus, the percentage of Priority NOCs was calculated as a fraction of the combined total of NDS and SNDS (ANDS and SANDS were excluded). This is summarized by Equation 13:

$$\%\ \text{Priority} = \text{Priority}\ /\ (\text{NDS}+\text{SNDS}) \qquad \textit{Eq. 13}$$

The total number of non-priority NOCs was calculated for each year, 2001-2008 inclusive. We subtracted the total number of Priority Review NOCs from the combined total of NDS and SNDS for each year:

$$\text{Non-Priority} = (\text{NDS}+\text{SNDS}) - \text{Priority} \qquad \textit{Eq. 14}$$

The percentage of non-priority NOCs was taken as a fraction of combined total NDS and SNDS for each year:

$$\%\ \text{Non-Priority} = \text{Non-Priority}\ /\ (\text{NDS}+\text{SNDS}) \qquad \textit{Eq. 15}$$

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43 Health Canada Personal Communication, *supra* note 31.

44 *Ibid.*

Finally, we analyzed whether NOC/*c* granted during the test period had their conditions met. This was done using the NOC database by following appropriate links through the "NOC/*c* conditions" box, entering "Prescription Pharmaceutical" in the Product Type field and entering January 1, 2001 to December 31, 2008 in the date field. This procedure yielded all NOC/*c* granted during the test period, from which we subtracted administrative NDS NOCs, as described above. The resulting list provides the drug name, drug manufacturer, NOC date, medicinal ingredient, NOC/*c* status, and information stating if and when the conditions were met.

Data were tabulated and analyzed using Microsoft Excel® (Microsoft. Corp., Redmond, WA), GraphPad Prism® (Graphpad Software Inc. La Jolla, CA), and SigmaPlot® (Systat Software, Inc. San Jose, CA). GraphPad or SigmaPlot were used to graph data, calculate linear regressions and exponential fits, and obtain R^2, time constants, slopes, and *P* values. Solid lines in Figs. 4-10 represent linear regression fits to the data with the exceptions of Figs. 8C, 9A, and 9B, which were fit to exponential functions as described in the Results.

C. Results

The number of NDS NOCs for 2001-2008 inclusive (test period) was 52, 26, 46, 62, 36, 54, 37, and 25 per year, respectively. As illustrated in Fig. 4A, the number of NDS NOCs issued over the test period declined slightly in the presence of stochastic fluctuations. When calculated as a percentage of total brand name and generic submissions (NDS, SNDS, ANDS, and SANDS), a similar trend was seen over the test period (Fig. 4B), from approximately 20% of total NOCs in 2001 to 8% in 2008. When expressed as a fraction of total brand name submissions only (NDS and SNDS), the general trend was also toward a slight decline in NDS NOCs during the test period (Fig. 4C), around an average of about 25% of total brand name submissions.

The total number of SNDS NOCs issued in the period 2001-2008 was 118, 80, 149, 138, 102, 137, 167, and 161 respectively. As illustrated by the data in Fig. 5, supplementary brand name submissions generally increased over the course of the test period. The total number of SNDS NOCs increased by approximately 60% during the period 2001-2008, though there is significant scatter in the data when administrative NOCs are removed (Fig. 5A). SNDS NOCs expressed as a percentage of total brand name NOCs issued (NDS and SNDS) also increased over the test period (Fig. 5C). The increase in the number and percentage SNDS NOCs can be compared with the relative lack of change in SNDS approvals when expressed as a fraction of all NOCs (Fig. 5B).

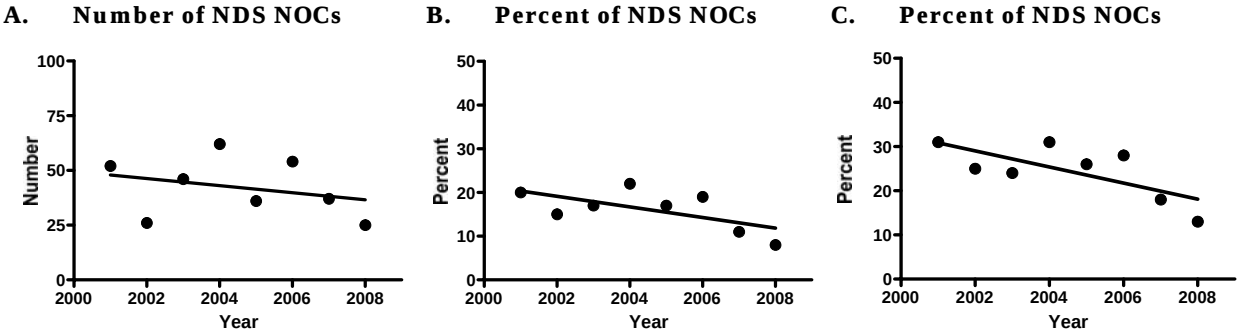

Fig. 4 (A) Number of NDS NOCs and **(B)** percent of NDS NOCs as a percent of all NOCs (NDS, SNDS, ANDS and SANDS) and **(C)** as a percent of NDS and SNDS only. Data in this and all other figures and tables are for calendar years 2001-2008 inclusive. Fits to the data are described in detail in the Methods and text. Abbreviations for this and all other figures are provided at the beginning of the text.

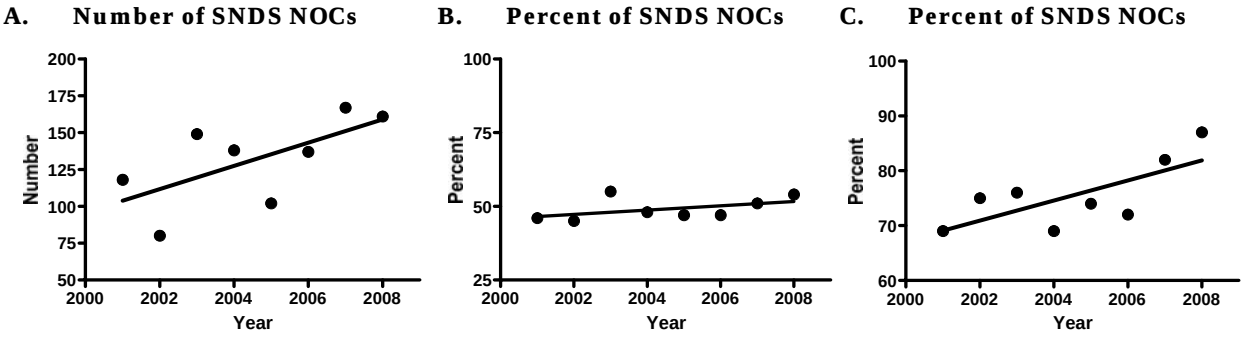

Fig. 5 (A) Number of SNDS NOCs and **(B)** SNDS NOCs as a percent of all NOCs (NDS, SNDS, ANDS and SANDS) and **(C)** SNDS NOCs as a percent of NDS and SNDS only.

Consistent with data for NDS NOCs, NOCs directed to NASs for the period 2001-2008 showed a slight decrease. The number of approvals for NASs per year was 21, 16, 16, 15, 12, 16, 20, and 14 during the test period. Figure 6A shows a declining trend, with significant scatter around an average of about 16 per year. The scatter is reduced when NAS NOCs are expressed as a percent of total NOCs. Figure 6B demonstrates that the percentage of approvals for NAS NOCs was a small fraction of total NDS and SNDS approvals (10%) and that this fraction remained relatively constant during the test period. Along with the decline in NDS NOCs (Fig. 4) and reciprocal increase in SNDS NOCs (Fig. 5), the data in Fig. 6 reveal that brand name pharmaceutical firms are focusing less on new drug submissions and more on follow-on supplementary submissions, even when the broad scope of Health Canada's NAS definition is taken into account.

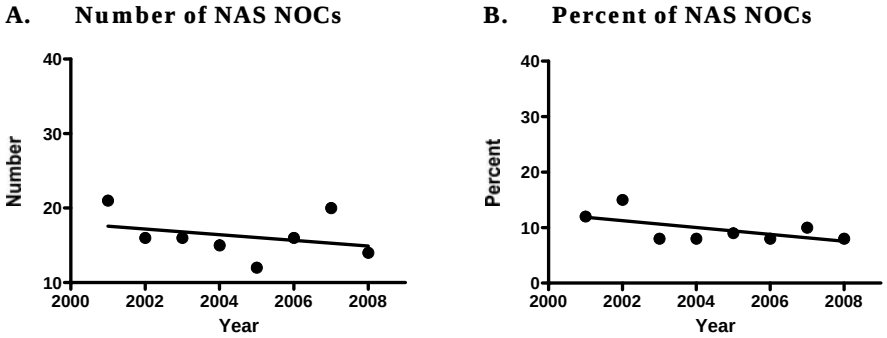

Fig. 6 (A) Number and **(B)** percent (all NDS and SNDS NOCs) of NAS NOCs.

Figure 7 illustrates trends in market approvals issued to generic firms. The total number of NOCs in the ANDS category was 73, 57, 60, 67, 64, 75, 98, and 90 over the test period. As shown in Fig. 7A, the trend was toward an increase in ANDS approvals, from a low of 57 in 2002 to a peak of 98 in 2007. This represents an increase in ANDS NOCs of about 72% over 5 years. ANDS approvals represented a fairly constant fraction of total NOCs issued over the test period, accounting for about a quarter of all NOCs issued by GOC (Fig. 7B). The total number of generic supplemental NOCs also increased over the test period (11, 16, 16, 19, 13, 25, 24, and 24). As illustrated in Fig. 7C, the number of SANDS NOCs more than doubled over this time frame, from a low of about 10 approvals per year in 2001 to a high of about 25 per year in 2007. This trend did not change when the data are expressed as a fraction of total NOCs (NDS, SNDS, ANDS, and SANDS) issued yearly over the test period (Fig. 7D). Thus, the number of supplemental submissions by both brand name (Fig. 5) and generic firms (Fig. 7) is increasing significantly with time.

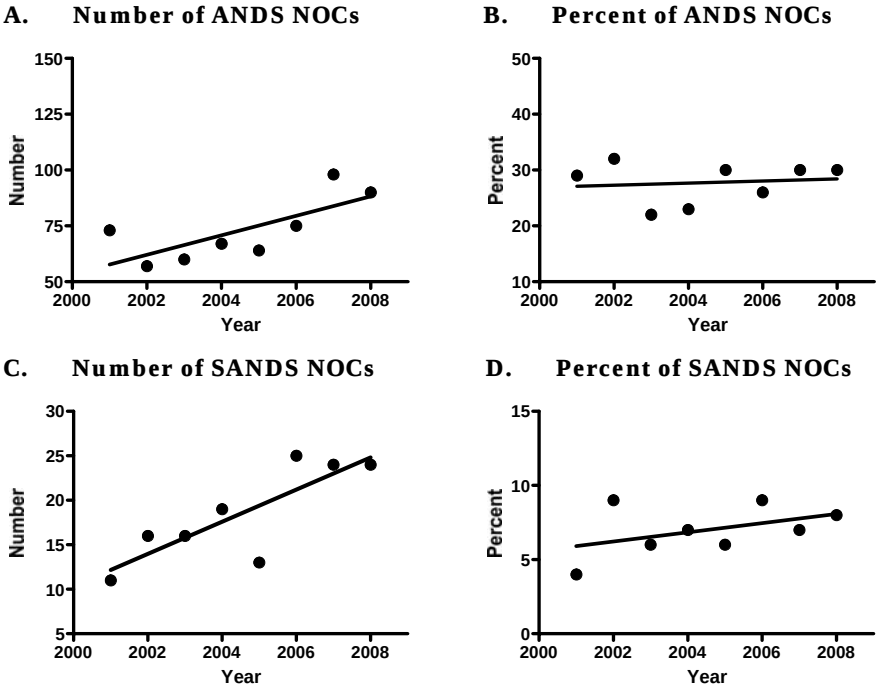

Fig. 7 Number of and percent of all NOCs (NDS, SNDS, ANDS and SANDS) of ANDS **(A and B)** and SANDS **(C and D)**.

Results obtained using the method outlined in Section I.B for determining the number of First in Class and Me Too NOCs are given in Fig. 8. The number of First in Class NOCs within the NDS category was 12, 7, 5, 7, 9, 8, 9, and 8 during the test period. Figure 8A shows that the number of these approvals was relatively constant over the period 2001-2008, within a range of 5-12 per year. As illustrated in Fig. 8B, the number of Me Too NDS NOCs decreased slightly over the test period, with a significant amount of scatter in the data around an average of about 34 approvals per year. The number of calculated Me Too NDS NOCs during the period 2001-2008 was 40, 19, 41, 55, 27, 46, 28, and 17.

A substantially different situation was observed with the calculated First in Class and Me Too SNDS data. As illustrated in Fig. 8C, the number of First in Class SNDS NOCs increased substantially over the test period, from a low of 1 in 2001 to a high of 22 in 2008 (1, 1, 6, 7, 4, 13, 19, and 22). We used two methods to calculate the time-dependence, slope, and potential non-linearities in the data set. For simplicity's sake, we present these in reverse order of statistical conservatism. For the first method, the data were fit to a single exponential function of the form $y = a \cdot exp^{(t/b)}$, where a is amplitude and b is the time constant. Both a and b were treated as free variables, and the fit was only to the time period 2001-2008. R^2 (squared correlation coefficient), representative of the 'goodness of fit' of the function to the data (0-1), was 0.92. This suggests significant acceleration of the increase in follow-on First in Class approvals over time. The second method entailed the use of a linear model. We found that 86% of the variation in Fig. 8C could be described linearly (P=0.000938) as opposed to non-linearly. Given the results of the exponential fit however, we also tested for a quadratic non-linearity using an ordinary least squares regression. While this increased the coefficient of determination to 92%, the squared term was not statistically significant at $P \leq 0.05$ (P=0.102153). However, given that there are only eight observations, it is possible we are faced with the cliché that "an absence of evidence is not the same as evidence of absence." While it was not possible to provide evidence for a non-linear term using both statistical methods, there clearly is enough of a trend to warrant further investigation as more data become available.

The number of Me Too SNDS NOCs issued during the test period also increased significantly (Fig. 8D), though not as dramatically as First in Class SNDS NOCs. There was an approximate doubling of

Me Too SNDS NOCs over the period analyzed, from a low of 79 in 2002 to a high of 148 in 2007. Along with the data in Figs. 4-6, these results demonstrate a significant trend for domestic brand name pharmaceutical firms to concentrate their efforts on supplementary Line Extension-type submissions rather than on new NDS, NDS NAS, or even NDS Me Too-type submissions.

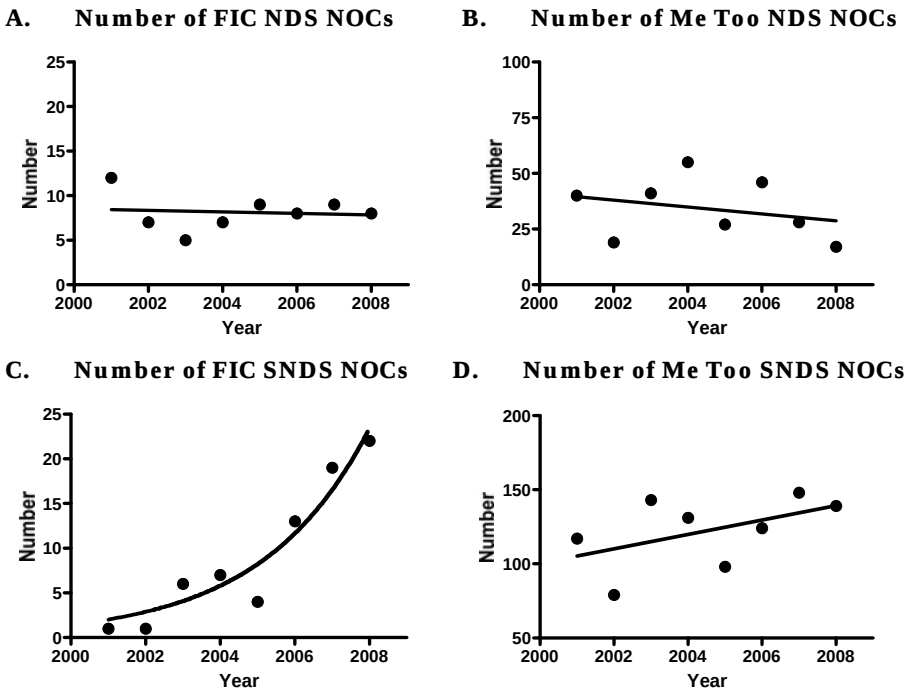

Fig. 8 Number of **(A)** First in Class (FIC) NDS NOCs, **(B)** Me Too NDS NOCs, **(C)** First in Class SNDS NOCs and **(D)** Me Too SNDS NOCs.

Figure 9 shows the time-dependence of drug approval via the two expedited approval streams (NOC/*c* and Priority Review) over the test period. The total number of NOCs issued under the NOC/*c* policy was 2, 3, 4, 3, 6, 13, 10, and 10 per year during the period 2001-2008. The data illustrate that the increase in NOC/*c* approvals occurred in a strongly time-dependent manner, independent of whether the data were expressed in absolute terms (Fig. 9A) or as a fraction of total brand name submissions (Fig. 9B). Using the first method described for analyzing data in Fig. 8C, the data could be fit to a single exponential function with R^2 values of 0.7 and 0.6 for Figs. 9A and 9B, respectively. The linear model on the other hand did not provide a strong suggestion for a non-linear term. The coefficient of determination for the simple ordinary least squares fit was 74% and 65% for Fig. 9A and 9B, respectively. However, the squared terms were not statistically significant (P= 0.976373587 and 0.712446789, respectively). Even so, the data clearly demonstrate a substantial increase in grant of NOC/*c* approvals over the test period, with an increase from a low of 3 in 2001 to a high of 13 in 2006 (650%, stabilizing at 500% in 2007 and 2008). The fraction of total NOCs represented by NOC/*c* approvals increased from a nominal value of about 1% in 2001 to a peak of 7% of all NOCs issued by Health Canada to brand name firms in 2006 (stabilizing at 5% in 2007 and 2008). As such, there is good evidence favouring a positive time-dependent increase in NOC/*c* approvals over the test period using both statistical methods. There is some evidence from the exponential fits supporting acceleration of this trend (R^2= 0.7 Fig. 9A; 0.6 Fig. 9B), but the trends are not as strong as that reported for Fig. 8C (R^2= 0.92) and differ from the results of the ordinary least squares analysis.

The data in Figs. 9A and 9B contrast significantly with the Priority Review data set, where both the absolute number (Fig. 9C) and fraction of total (Fig. 9D) NOCs that were issued under the Priority Review stream decreased over the period 2001-2008 (13, 9, 5, 5, 8, 7, 9, and 5 per year). In comparison, non-Priority Review NOCs increased slightly over the test period, expressed either in absolute terms

(Fig. 9E) or as a fraction of total NOCs issued (Fig. 9F). Indeed, comparison of data in Figs. 9A-9D demonstrate that while the number and percentage of Priority Review NOCs exceeded those for NOC/*c* approvals in 2001 by two-fold, both trends were completely reversed by 2008. Given the relative lack of change in the fraction of total NOCs that were subject to Priority Review (Fig. 9F), the data in Fig. 9 demonstrate that brand name firms have been highly successful in facilitating early access via the NOC/*c* limb of the expedited stream.

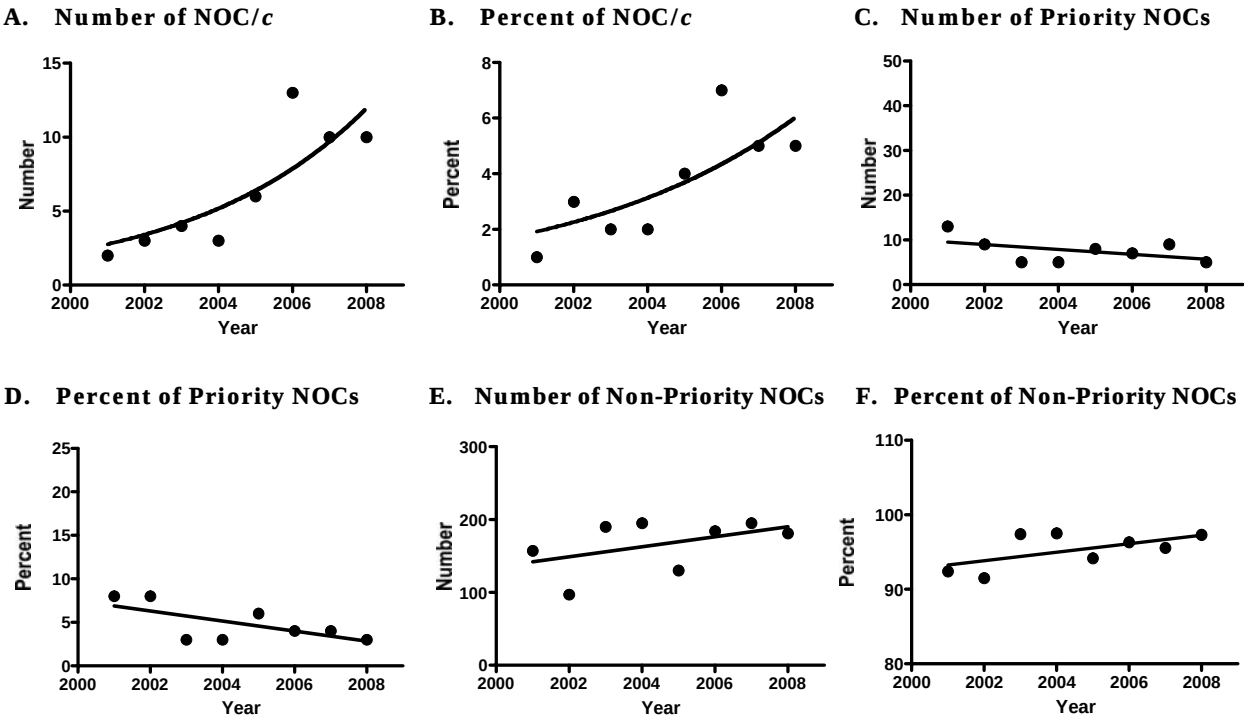

Fig. 9 Number and percent (percent of all NDS and SNDS NOCs) of NOC/c **(A and B)**, Priority NOCs **(C and D)**, and Non-priority NOCs **(E and F)**.

Data relating to whether or not the "conditions" associated with NOC/*c* approval were actually met during the test period are given in Fig. 10 and Table 3. Figure 10A depicts the number of NOC/*c* approvals issued per year that *eventually* had their conditions met: the filled portion of each bar represents the number of NOC/*c* approvals issued in a given year that had their conditions met, while the unfilled portion represents the number of NOC/*c* approvals granted in a given year that have not yet had their conditions met to date (i.e. filled and unfilled portions represent the fraction of total NOC/c with conditions met and unmet, respectively). For example, in 2001 two NOC/*c* approvals were granted: one had its conditions met in 2004 and one has not yet had its conditions met. Therefore the bar is half filled. In 2002, three NOC/*c* approvals were granted, and all three have not yet had their conditions met. The data in Fig. 10A suggest a significant positive trend toward NOC/*c* approvals not having their conditions met during the test period, at least in the short period of time since issuance.

TABLE 3. DATE OF NOC/C GRANT AND DATE CONDITIONS ASSOCIATED WITH NOC/C WERE MET DURING THE PERIOD 2001-2008

Year	NOC/*c* (Date of Grant)	Conditions Met NO	Conditions Met YES
2001	2001-03-01	--	2004-07-5 (n=1)
	2001-09-20	NOT met to date (n=1)	--
2002	2002-05-28; 2002-08-07; 2002-11-25	NOT met to date (n=3)	--
2003	2003-03-18	--	2005-07-20 (n=1)
	2003-07-07; 2003-10-08; 2003-12-17	NOT met to date (n=3)	--
2004	2004-06-30	--	2008-12-02 (n=1)
	2004-06-02;2004-12-08	NOT met to date (n=2)	--
2005	2005-01-27; 2005-11-01; 2005-12-07	--	2007-09-11; 2008-12-02; 2008-10-23 (n=3)
	2005-04-01; 2005-04-15; 2005-12-29	NOT met to date (n=3)	--
2006	2006-04-24; 2006-05-12	--	2007-09-11; 2008-06-06 (n=2)
	2006-05-03; 2006-06-16; 2006-06-26; 2006-07-18; 2006-07-28; 2006-07-28; 2006-08-17; 2006-10-06; 2006-10-18; 2006-11-07; 2006-12-14	NOT met to date (n= 11)	--
2007	2007-03-01; 2007-03-26; 2007-05-24; 2007-08-01; 2007-09-12; 2007-09-22; 2007-11-09; 2007-11-27; 2007-11-30; 2007-12-20	NOT met to date (n=10)	--
2008	2008-01-17; 2008-03-03; 2008-05-02; 2008-06-18; 2008-07-23; 2008-09-09; 2008-09-30; 2008-10-15; 2008-12-09; 2008-12-19	NOT met to date (n=10)	--
TOTAL	**N= 51**	**N= 43**	**N= 8**
PERCENT	**100%**	**84.3%**	**15.7%**

Figure 10B shows the same data expressed as the year in which conditions for NOC/*c* approvals were met *independent of the year* NOCs were granted. Whereas Fig. 10A is focused on the year NOC/*c* approvals were issued, Fig. 10B is focused on the year conditions were met. Note that the Y axis is set slightly (-0.25) below zero. This was done in order to ensure years where no conditions were met were still represented by an observable bar. For example, in 2001, 2002, 2003, and 2006 no NOC/*c* licences that were issued within the test period had their conditions met. This can be contrasted with data from 2004, 2005, 2007, and 2008, where 1, 1, 2, and 4, NOC/*c* approvals ultimately had their conditions met. Unlike data in Fig. 10A, which appear to indicate a trend toward increasing non-compliance, the data in Fig. 10B demonstrate a smaller yet parallel trend toward an increased likelihood that conditions attached to an NOC/*c* were met over the test period.

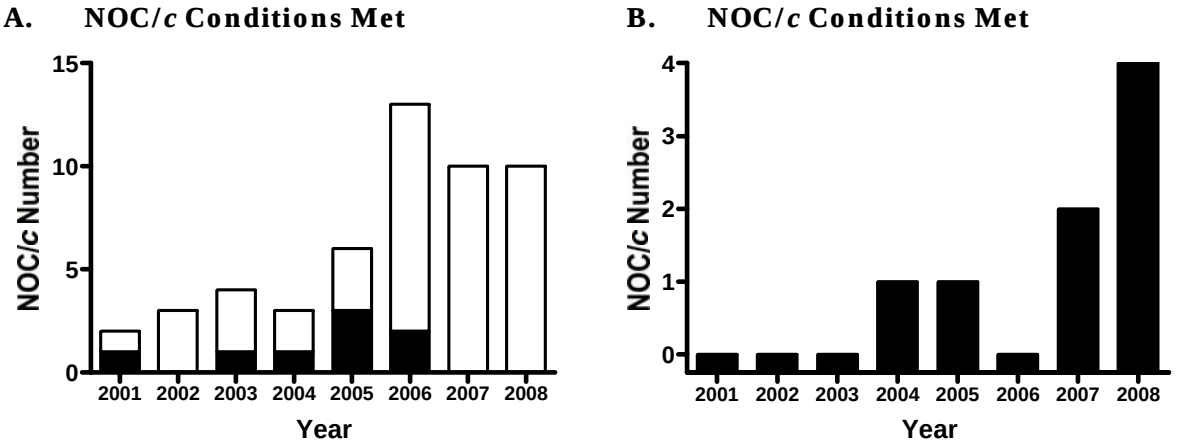

Fig. 10 Number of NOC/c granted by GOC during the 2001-2008 test period that had their conditions met. **(A)** Filled bar portions represent the number of NOC/*c* issued in that calendar year that eventually had their conditions met. Unfilled bars represent NOC/*c* issued in that year which have not yet had their conditions met to date. **(B)** Year in which conditions attached to NOC/*c* were met independent of the year NOCs were granted.

Finally, we analyzed the number of NOCs approved during the period 2001-2008 that were withdrawn for safety reasons.[45] The data in Table 4 illustrates that a very small percentage of NOCs issued during the test period have been withdrawn in Canada to date.

These data can be parsed in two ways: first, as withdrawn NOCs (n=10) expressed as a fraction of total NOCs (n=2,122) granted over the test period; and second, as withdrawn products (n=4) expressed as a fraction of total products (n=608) associated with the larger number of NOCs. For the first procedure, 2,122 NOCs were issued over the test period, 10 of which were withdrawn within the same time frame. This amounts to 0.47% issued NOCs that were withdrawn. However, this value is somewhat misleading because consumers do not purchase NOCs. Rather they purchase and consume, and drug agencies typically regulate, drug products. Of 608 products receiving NOCs during the course of the test period, only four were withdrawn (Gatifloxacin, June 29, 2006; Lumaricoxib, October 3, 2007; Tegaserod, March 30, 2007; Valdecoxib April 7, 2005). This amounts to a small percentage (0.66%) of marketed products issued in the test period that were subsequently withdrawn for safety reasons within the same time frame.

Withdrawals in Canada were slightly higher than withdrawals for the same drug pool in at least two comparator jurisdictions (0.2%, U.S.; 0%, France). However, of the total number of products or NOCs withdrawn in Canada for safety reasons during the test period (n=4), none were withdrawn in the two expedited streams (NOC/*c*, Priority Review). Data were drawn from published studies in Canada,[46] the U.S.,[47] and France.[48]

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45 A drug withdrawal or recall has the effect of removing a health product, such as a prescription or non-prescription pharmaceutical, from the marketplace. On its website, Health Canada addresses the issue of safety and drug withdrawals and states that "Health Canada posts safety alerts, public health advisories, warnings, recalls, press releases, and other notices from industry on marketed health products, including Natural Health Products and medical devices". Health Canada, "Drugs and Health Products—Advisories, Warnings and Recalls", online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index-eng.php> (The website elaborates by saying "this service to health professionals, consumers, and other interested parties informs and educates Canadians about new health risks associated with the use of certain marketed health products. Recalls are initiated by importers and manufacturers after recognizing that there may be a safety concern related to a specific health product. Health Canada works with the health product industry to ensure hazardous products are removed from the marketplace in an effective and efficient manner").

46 Joel Lexchin, "Drug Withdrawals from the Canadian Market for Safety Reasons, 1963-2004" (2005) 172 Canadian Medical Association Journal 765 [Lexchin, "Withdrawals"]. Updated via Personal Communication with Joel Lexchin, September 23, 2008 and March 4, 2009; Health Canada, "Drugs and Health Products—Past Advisories, Warnings and Recalls", online: Health Canada <http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>.

TABLE 4. DRUG WITHDRAWALS FOR EXPEDITED AND STANDARD REVIEW STREAMS FOR NOCS APPROVED 2001-2008 IN CANADA AND COMPARATOR JURISDICTIONS.

SUBMISSION CLASS	NOC ISSUED	WITHDRAWALS (Country)		
	CANADA	CANADA	U.S.	FRANCE
	2001-2008	2001-2008[46]	2001-2007[47]	2001-2008[48]
A. Expedited				
NOC/*c*	51	0	0	0
Priority Review	61	0	0	0
B. Standard				
NDS	338	4	1	0
SNDS	1,052	0	0	0
ANDS	584	0	0	0
SANDS	148	0	0	0
TOTAL	2,122	4	1	0

II
DISCUSSION

Data from the qualitative and quantitative analyses undertaken here suggest that concerns expressed over PLF pushing Canada in a new direction concerning the workings and output of its drug regulatory regime may be somewhat overstated. The data demonstrate that the approval mechanism enshrined in the existing *Food and Drugs Act* and *Food and Drug Regulations* already anticipates the lifecycle approach, at least as it is described in the *Blueprint*,[49] PLF Concept Paper,[50] and Bill C-51.[51] Analysis of eight years of GOC approval statistics shows that new drug submissions have been on the decline for at least this long, while supplementary submissions from both brand name and generic firms during this time have conversely increased. Moreover, Priority Reviews, which have the same or similar evidentiary requirements as standard review submissions, declined slightly over the period analyzed. By contrast, NOC/*c* submissions, which have reduced front-end evidentiary requirements compared to standard submissions, increased substantially. Thus, despite little or no change in the unmet medical needs of the Canadian population, a relatively small but significant percentage of drugs have entered our national market increasingly earlier in their product development lifecycle. The data further imply that the Canadian pharmaceutical industry as a whole may be "doing more with less". This conclusion applies to both the rate and direction of innovative activity undertaken by brand name and generic firms. New or standard drug submissions are flat while supplementary and generic submissions have increased substantially. Even approvals for Me Too drugs remained relatively constant or slightly elevated when compared to Line Extensions and new uses. The data reveal a trend away

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47 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. Updated March 4, 2009 using information from U.S., Food and Drug Administration, "Index to Drug-Specific Information", online: FDA <http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm>.

48 Pascale Olivier & Jean-Louis Montastruc, "The Nature of Scientific Evidence Leading to Drug Withdrawals for Pharmacovigilence Reasons in France" (2006) 15 Pharmacoepedimiology and Drug Safety 808 (Updated via Personal Communication with Pascale Olivier, September 28, 2008 and March 4, 2009).

49 Health Canada, "Blueprint for Renewal: Transforming Canada's Approach to Regulating Health Products and Food" (October 2006), 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"].

50 Health Canada, "The Progressive Licensing Framework Concept Paper for Discussion", online: Health Canada <http://hc-sc.gc.ca/dhp-mps/homologation-licensing/develop/proglic_homprog_concept-eng.php> [Health Canada, "Concept Paper"].

51 *Bill C-51*, *supra* note 5.

from development of novel "breakthrough" pharmaceuticals over the course of the test period. Results of this nature may provide an example of policy resistance,[52] whereby government policy inhibits or prevents the very thing it seeks to facilitate through the unintended consequences of its action(s).[53]

A. Interpretation of Data

Our analysis of NOCs issued in Canada in the period 2001-2008 yields a number of major observations relevant to PLF. First, the data demonstrate that the current drug regulatory regime already anticipates the lifecycle approach. Second, it provides insight into the types of drug submissions that are likely candidates to receive expedited drug approval under the terms of flexible departure. Third, the data speak to the issue of innovation patterns in the area of pharmaceutical development. Together, the data have important implications for the manner in which PLF is likely to be rolled out, the types of drugs that the public are likely to see on the market in the near future, and those drugs with which they are likely to be provided in the long term, absent significant changes in IPR rights associated with drug approval and marketing.

Data generated in this study show that the existing regulatory system in Canada is already moving in a direction consistent with what is proposed under the PLF system: that is, toward earlier access to drugs that occupy the "extraordinary need" niche with emphasis on post-market surveillance. This is most clearly exemplified by the NOC/*c* data set, expressed either as the number of NOC/*c* or as a fraction of total NOCs (Figs. 9A and 9B). As described in the Results, while the absolute number of NOC/*c* approvals is relatively small (peaking at 13 in 2006), the number when expressed as a function of total brand name NOCs granted by GOC is not insignificant (7%). Moreover, it is evident that the fractional number of NOC/*c* approvals is increasing significantly over time (from 1% in 2001 to 7% in 2006) and that this increase is occurring in a strongly time-dependent manner (Figs. 9A and 9B). The trend toward increasing NOC/*c* approvals is occurring despite a slight downward trend in new drug submissions expressed either in absolute terms (Fig. 4A) or as a function of total brand name submissions (Fig. 4C). Even more dramatically, the escalation in NOC/*c* approvals has been accompanied by a reverse trend in Priority Review NOCs (compare Figs. 9A and 9C). Since the NOC/*c* policy issues NOCs faster and under the condition that additional post-market authorization safety and/or efficacy studies are undertaken, there is an overall increase of drugs that are being authorized in a similar manner to that contemplated by Health Canada in the *Blueprint* and PLF Concept Paper policies and in Bill C-51.

The data also suggest that the trend toward flexible departure is being accompanied by a small but significant trend for sponsors to meet conditions associated with NOC/*c* approval (Fig. 10B). This conclusion is tempered however by the large number of outstanding NOC/*c* approvals where the conditions have not yet been met (Fig. 10A; Table 4). A second caveat is the fact that there is not a great deal of data in this regard given the gap between issuance and conditions met in later years which does not apply to analysis of approvals per se. The observation that an increasing number of drugs are being made available to the public under the circumstance that they meet certain conditions in order to maintain market authorization demonstrates that Health Canada is already approving drugs with PLF in mind. Positively, none of these drugs have been recalled for safety reasons to date (Table 4).

Of interest, the data show that the number and fraction of total NOCs issued under the Priority Review policy have steadily declined over the test period (Fig. 9C). The number has hovered fairly constantly around 7 or 8 per year (Fig. 9C) compared with increases in the number and fraction of non-

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[52] John D. Sterman, "All Models Are Wrong: Reflections on Becoming a Systems Scientist" (2002) 18 Systems Dynamics Review 501 [Sterman, "Reflections"].

[53] In *AstraZeneca Canada Inc. v Canada (Minister of Health)*, 2006 SCC 49, [2006] 2 S.C.R. 560 at para. 39, Justice Binnie stated that it is "entirely understandable" that brand name pharmaceutical firms avail themselves of loopholes in the *NOC Regulations* that permit ever-greening of older products by "adding bells and whistles" to them after the original patent has expired. See also 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"]; 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"]; See also 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. of Sci. & Tech. L. 120 [Bouchard, "Balancing"]

priority NOCs (Figs. 9E and 9F). At first glance, this might seem inconsistent with the notion that GOC is anticipating PLF. For example, given that progressive licensing is partially geared toward enhanced access, it only seems logical that NOCs issued under Priority Review should also be increasing. On more careful examination however, it is evident that a decreasing number of Priority Reviews is anticipatory of PLF. The policy for fast-tracking eligible NDS and SNDS is intended to provide enhanced availability of products for the treatment, prevention, or diagnosis of serious, life-threatening, or severely debilitating diseases or conditions where there is an unmet medical need or for which a substantial improvement in the benefit/risk profile of the therapy is demonstrated.[54] Unlike the NOC/*c* policy, Priority Review is aimed at getting drugs approved faster *without* a change in the amount of scientific evidence required for approval prior to market entry. According to leadership at Health Canada, this ensures that drug manufacturers jump ahead of others in the approval queue.[55] Moreover, Priority Review policy, unlike the NOC/*c* policy, does not demand that sponsors conduct post-marketing studies as a means to continue or maintain the NOC. Priority Review is essentially a fast-tracking mechanism without any further evidentiary obligations imposed on industry. This might be seen to accord less with PLF policy than the NOC/*c* mechanism. While both streams promote faster drug approval, only the latter is centered on the lifecycle approach, which demands that in return for faster drug approval, a drug's safety and efficacy must be subject to legal scrutiny beyond initial market authorization. Thus, it is reasonable to speculate that in anticipation of the PLF regime, Health Canada might shift somewhat away from the Priority Review stream as the primary means of enhancing access toward the NOC/*c* stream.

Anticipation of PLF and consequently faster drug approval is also evident by other trends in the data set. For instance, the percentage of NDS NOCs decreased over the test period (Fig. 4B) whereas the number (Fig. 5A) and fraction (Fig. 5B) of supplemental submissions increased. SNDSs are also known as "Line Extensions" of previously existing products, usually involving changes to a pre-existing drug such as a change in the route of administration (e.g., oral to intravenous), dosage form (e.g., tablet to capsule), salt form (e.g., besylate to mesylate), or indication (e.g., antidepressant to anxiolytic). For the most part, getting a Line Extension or SNDS onto the market is a faster process compared with drugs approved via the new drug submission stream. This is true even where approval times for SNDS and NDS are roughly equal, as production and marketing of Line Extension products takes less time than producing and marketing truly new drugs, owing to manufacturing experience and related competencies. Thus, an increasing number of yearly SNDS NOCs is indicative of a general focus on faster access, if not faster approval. This conclusion is supported by the observation that the number of New Active Substances (NAS) is decreasing over time (expressed either in absolute terms (Fig. 6A) or as a fraction of total brand name NOCs (Fig. 6B) issued), particularly given the broad NAS definition employed by GOC.

The present data also have important implications for the rate and direction of innovation by domestic pharmaceutical firms. For example, approvals relating to both types of NDSs (Fig. 4) declined over the test period. By comparison, the number of supplemental submissions increased when expressed either in absolute terms (Fig. 5A) or as a fraction of total brand name submissions (Fig. 5C). Together, the data indicate that pharmaceutical companies are increasingly doing more with less, implying that firms are expending fewer and fewer resources on developing breakthrough drugs and more on extending the utility of already existing products. This trend is also demonstrated by the decreasing number of NAS NOCs with time (Fig. 6), because drugs in this group include those that differ minimally from pre-existing drugs such as salts, enantiomers, and other derivatives of already marketed compounds. Furthermore, the number of SNDS deemed to be First in Class by virtue of new indications escalated in a strongly time-dependent, and potentially non-linear (R^2= 0.92, Fig. 8C) manner. Brand name pharmaceutical firms are therefore strongly concentrating their efforts on getting as much value as possible from their existing drug development activities rather than focusing on development of first-in-kind products. The data are in line with results from Health Canada indicating that there has been a 225% increase in the number of clinical trial applications since 2001, compared with only a 19%

54 Health Canada, "Priority Review Guidance Document", *supra* note 23.
55 Health Canada Personal Communication, *supra* note 31.

increase in firm R&D spending over a similar time period.[56] A parallel conclusion arises from the analysis of generic NOC data. For example, we found that the number of ANDS and SANDS yielding NOCs during the test period increased substantially. This was true independent of whether the data were expressed in absolute terms (Figs. 7A and 7C) or as a percentage of total NOCs (Figs. 7B and 7D). The increase in the number of ANDS (75%, Fig. 7A) and SANDS (100%, Fig. 7C) NOCs was greater than the corresponding increase in NDS (no change, Fig. 4A) and SNDS (15%, Fig. 5A) NOCs. Absolute values for ANDS and SANDS are expected to reflect the increasing release of generic drugs into the market as the number of drugs that come off patent protection under the *NOC Regulations* increases. This trend is reflected in the data expressed as a fraction of total NOCs (Figs. 7B and 7D) as well.

One of the most intriguing findings of the study is that the number of new Me Too (Fig. 8B) and First in Class (Fig. 8A) NDS NOCs decreased slightly over the test period. By contrast, the number of follow-on Me Too SNDS (Fig. 8D) and First in Class SNDS (Fig. 8C) NOCs increased significantly. Me Too SNDS NOCs in particular doubled over the test period. Moreover, First in Class SNDS NOCs increased in a strongly time-dependent manner, from 1 to 22. The slope of this increase well exceeds even that for generic supplemental submissions (Fig. 7C). These data provide support for the conclusion that the Canadian domestic pharmaceutical industry is "doing more with less." Brand name firms in particular appear to be expanding the market exclusivity duration of existing products, though firms obviously need to get on the market with at least one new compound in a given chemical class prior to expansion via SNDS. Together with data showing a decline in all types of new or standard submissions by brand name firms (Figs. 4C, 6A, 8A, and 8B) and an increase in other types of supplementary submissions assessed (Figs. 5C, 8C, and 8D), the results suggest that (a) the Canadian pharmaceutical industry, as a whole, is expending fewer of its resources on developing novel "first-of-kind" technologies and more on leveraging existing technologies and (b) that technology appropriation is alive and well in Canada.[57]

B. Study Limitations

1. *Empirical Considerations*

The study is limited by the restrictions typical of empirical studies. First, data analyzed were only those for the test period. The year 2001 was chosen as our starting point, as this was the date when substantial amendments to Canadian drug regulation were made that affected both the mechanisms and speed of approval.[58] Second, there is significant scatter of the data from one year to the next which impeded a more strongly powered analysis. For example, we not only obtained yearly means as reported in Figs. 1-10, but also calculated quarterly bins for each year in order to improve the statistical power in linear and non-linear analyses. However, we could not use this data owing to a small trend towards quarterly differences in the data set e.g., there was a trend towards more approvals granted in the third and fourth quarters of each year. However, this trend did not reach statistical significance, necessitating the use of yearly averages. As a consequence, both sample sizes and statistical power were reduced. Finally, while we obtained and analyzed approval data independently rather than using GOC Annual Reports, we were nevertheless limited to the results reported by Health Canada.[59] Equally important, our analysis was dependent on Health Canada's method of determining the definition of an

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[56] Health Canada: Health Products and Food Branch, "Clinical Trials Regulatory Review—Stakeholder Workshop" (March 26, 2007), 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"].

[57] As used here, the term "appropriation" refers to a party's ability to capture profits generated from their own inventions or related inventions.

[58] Health Canada, "Stakeholder Workshop"*, supra* note 56 (according to Health Canada at 6, the objectives of the 2001 regulations were to "Shorten application review times without endangering health and safety; Improve safety mechanisms for research subjects; Regulator to be more involved in clinical trial monitoring and follow-up; Remove obstacles to additional R&D; Improve access to innovative therapies and advice from Canadian physicians with research experience").

[59] For an example of differences in the empirical analysis of a "partially" reported database vs. governmental analysis of a "full" data set, see Daniel Carpenter, Evan James Zucker & Jerry Avorn, "Drug-Review Deadlines and Safety Problems" (2008) 358 New Eng. J. Med. 1354 at 1360, the subsequent Letter to the Editor from FDA Officials and Correction by the authors: Clark Nardinelli, Michael Lanthier & Robert Temple, "Letter to the Editor" (2008) 359 New Eng. J. Med. 95; Daniel Carpenter, "Reply to Letter to the Editor" (2008) 359 New Eng. J. Med. 96 [Carpenter, "Reply"].

NAS, which in turn substantially influenced the methods used to calculate the number of First in Class and Me Too drugs. This is discussed in more detail below.

2. *Me Too and First in Class Criteria*

We acknowledge that the Compound-Indication method summarized in Table 2 yields a fraction of Me Too and First in Class drugs that may differ from methods used by other agencies. For example, the WHO Collaborating Center for Drugs Statistics Methodology[60] produces a different result as to what NOCs would have been classified as First in Class or Me Too, yielding more Me Too than First in Class NOCs. The reason for this discrepancy is that under the WHO methodology, compounds that are in the same chemical family as the original First in Class drug are all deemed to be Me Too drugs irrespective of whether they are directed to new indications. Table 5 illustrates this concept.

TABLE 5. WHO COMPOUND-INDICATION CLASSIFICATION

YEAR	COMPOUND/INDICATION	CLASSIFICATION
2000	Compound X (first 'X' Compound) with Indication A	First in Class
2001	Compound X with Indication B	Me Too
2001	Compund *a*X (Compound in the family of X) with Indication A	Me Too
2001	Compound *a*X with Indication B	Me Too
2001	Compound *x*X with Indication C	Me Too

However, the methods used to obtain the data in Table 5 differ from those used by Health Canada to classify NOCs, particularly in the SNDS category. The Health Canada methodology focuses not on chemical class but rather on indications. Nevertheless, assuming for the moment that the WHO classification is the right one for the purposes of this discussion, using it to analyze our data would have the effect of converting a certain number of supplemental First in Class SNDS NOCs to new Me Too NDS NOCs. While this might appear on the surface to shift emphasis from "supplemental" to "new" submission approvals, both Me Too NDS and First in Class SNDS NOCs are directed to products that are extensions of existing technologies, largely via new use indications, as opposed to first-of-kind technologies. Therefore, using the WHO framework would not alter our major observations and conclusions, including (1) that the pharmaceutical industry as a whole is doing more with less and (2) that an increasing number of drugs are being approved with significant post-marketing obligations over the test period, while NOCs in other expedited streams (e.g., Priority Review) have remained relatively constant or decreased slightly over the same time frame.

3. *Innovative Value of Me Too and Line Extensions*

We did not undertake a study of, nor are we offering a model for, innovation in the domestic Canadian pharmaceutical marketplace. Therefore, we provide definitions for neither "innovation" nor what constitutes an "innovative" therapeutic product. Rather, the point of the present study was to independently analyze several years of drug *approval* data, and to analyze the data from the perspective of the policies underpinning the emerging PLF regime. These include policies pertaining to safety and efficacy, expedited review (NOC/*c* and Priority Review), IPR rights, user fees, precautionary principle, etc.[61] Our concern, within the four corners of the present study, was whether NOCs were directed to (a) "new" active substances, "new" drug submissions, "first" in class drugs, "priority" review drugs, and drugs approved via the NOC/*c* stream versus, (b) "me too" drugs, "line extension" drugs, "abbreviated" generic submissions, and other "supplemental" submissions. We are mindful of the controversial nature of the debate surrounding the economic and therapeutic value of Me Too

[60] WHO Website, *supra* note 41.
[61] Bouchard & Sawicka, *supra* note 2.

and Line Extension drug products in Canada,[62] France,[63] the U.S.,[64] the E.U.,[65] and the U.K.,[66] as well as recent reports on the need to facilitate innovation[67] and generic competition[68] in the context of shifting drug approval and associated IPR rights regimes. We are also mindful of the tendency of certain technological and regulatory systems to experience "lock-in"[69] as a result of increasing returns,[70] and that the data described in this study may be a potential example of one or both of these processes. The relevance of our data to the issue of innovation in the pharmaceutical sector is the subject of a follow-up study currently underway on the empirical relationship between patterns of drug approval, patenting, and litigation. Finally, given that Canada and the U.S. are the only two jurisdictions with formal linkage regulations tying drug approval and drug patenting,[71] we have narrowed the interpretation of our empirical data and the associated literature review[72] to the North American context, as it is likely to be governed by emerging lifecycle regulation models.

C. Assessing the Lifecycle Approach: The Long View

In the companion article,[73] a number of concerns are reviewed that, when combined, have provided the impetus for substantial law reform in the area of drug regulation. These include considerations relating to the speed and mechanism of approval, the relation of the former to fee-for-service user fees, the relation of the latter to a shift from the precautionary principle to risk management principles, and an increase in the public-private partnership characteristic of the approval process, including govern-

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62 Joel Lexchin, "Intellectual Property Rights and the Canadian Pharmaceutical Marketplace: Where Do We Go from Here?" (2005) 35 International Journal of Health Services 237 at 243 [Lexchin, "IP Rights"]. See also Patented Medicine Prices Review Board Government of Canada, *Annual Report* 2000, online: Patented Medicine Prices Review Board <http://www.pmprb-cepmb.gc.ca/english/View.asp?x=113&mp=91> [*Patented Medicine Prices Review Board Annual Report*].

63 "Drugs in 2001: A Number of Ruses Unveiled" (2002) 11 Prescrire International 58 ["Drugs in 2001"].

64 James Love, "Evidence Regarding Research and Development Investments in Innovative and Non-Innovative Medicines" (Washington, Geneva & London: Consumer Project on Technology 2003), online: Consumer Project on Technology <http://www.cptech.org/ip/health/rnd/evidenceregardingrnd.pdf>; Song Hee Hong *et al.*, "Product-Line Extensions and Pricing Strategies of Brand Name Drugs Facing Patent Expiration" (2005) 11 Journal of Managed Care and Pharmacy 746. See also Joseph A. DiMasi and Cherie Paquette, "The Economics of Follow-on Drug Research and Development" (2004) 22: Suppl. 2 Pharmacoenomics 1.

65 Juan-José Ganuza, Gerard Llobet & Beatriz Dominguez, "R&D in the Pharmaceutical Industry: A World of Small Innovations" (2009) 55 Management Science 539.

66 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; see also John Abraham & Courtney Davis, "Deficits, Expectations, and Paradigms in British and American Drug Safety Assessments: Prising open the Black Box of Regulatory Science" (2007) 32 Science, Technology & Human Values 399; John Abraham, "Sociology of Pharmaceuticals Development and Regulation: A Realist Empirical Research Programme" (2008) 30 Sociology of Health and Illness 869.

67 U.S., Government Accountability Office, *New Drug Development: Science, Business, Regulatory and Intellectual Property Issues Cited as Hampering Drug Development Efforts* (Washington: United States Government Accountability Office, 2006), online: US GAO <http://www.gao.gov/new.items/d0749.pdf>; EC, DG Competition Staff, *Pharmaceutical Sector Inquiry: Preliminary Report* (28 November 2008); International Expert Group on Biotechnology, Innovation and Intellectual Property, "Toward a New Era of Intellectual Property: From Confrontation to Negotiation: A Report from the International Expert Group on Biotechnology, Innovation and Intellectual Property" (Montreal: 2008), online: The Innovation Partnership <http://www.theinnovationpartnership.org/data/ieg/documents/report/TIP_Report_E.pdf>.

68 Competition Bureau, *Benefiting from Generic Drug Competition in Canada: The Way Forward* (Ottawa: Public Works and Government Services Canada, 2008). See also Roy J. Romanow Commission on the Future of Health Care in Canada, *Building on Values: The Future of Health Care in Canada* (Ottawa: Public Works and Government Services Canada, 2002) [*Romanow*].

69 Timothy J. Foxton, "Technological Lock-in and the Role of Innovation" in G. Atkinson, S. Dietz & E. Neumayer, eds., *Handbook of Sustainable Development*, (Cheltenham, UK: Edward Elgar, 2006).

70 W. Brian Arthur, "Increasing Returns and the Two Worlds of Business" (1996) July-Aug. Harvard Business Review 100.

71 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" (2000) 55 Food & Drug L.J. 373 [Hore]; Andrew A. Caffrey & Jonathan M. Rotter, "Consumer Protection, Patents and Procedure: Generic Drug Market Entry and the Need to Reform the Hatch-Waxman Act" (2004) 9 Va. J.L. & Tech. 1 at 4-7. See also Rebecca S. Eisenberg, "Patents, Product Exclusivity, and Information Dissemination: How Law Directs Biopharmaceutical Research and Development" (2003) 72 Fordham L. Rev. 477; Bouchard, "Living", *supra* note 53.

72 Bouchard & Sawicka, *supra* note 2.

73 Bouchard & Sawicka, *supra* note 2.

ment vetting of increasing IPR rights associated with pharmaceutical products. The possibility exists that these issues have combined to result in more drug withdrawals, black box warnings, and dosage form discontinuations for safety reasons, and a significant expansion and acceleration of mortality and morbidity associated with high-profile drug withdrawals. The lifecycle approach has been criticized as only worsening many of these problems. This is particularly true of the focus on access at the cost of post-market safety and prolonged market monopolies on Line Extension and Me Too drugs. The results in this paper do little to ameliorate many of these concerns, as the data indicate GOC is already anticipating PLF in its current regulatory efforts and that pharmaceutical firms are increasing their focus on extending the lifecycle of existing products and technologies rather than inventing new breakthrough products.

We have referred to the rTPL innovation ecology here and in earlier work as an example of a dynamic, emergent, complex adaptive system. What makes a system complex as opposed to merely complicated is the strong nature of the interrelationships and interdependencies of the actors and institutions making up a system or network. In the manner of a spider web, tweaking one strand affects all other strands in the web. As noted by Gell-Mann,[74] complex systems are characterized by broad rules that have increasing applicability and universality as the symmetry and elegance of the rules increase. We believe this applies to innovation ecologies regulated by law,[75] particularly where large-scale public and private rights must be balanced. In order to assess the legitimacy of PLF as a regulatory tool in service of a highly complex and adaptive pharmaceutical, clinical, economic, and political system, one must therefore look to both sides of the access-safety equation to see what value PLF has for so-called adaptive[76] or robust[77] policy-making. Too narrow a focus on access or post-licensing obligations can only lead to a viewpoint that will miss critical information that arises outside of its bandwidth. PLF is expressly intended to replace static, linear, one-sided, front-loaded, and time-locked models of drug development and regulation. Its legitimacy should be assessed that way, hence the need for the "long view".

On one side of a shifted evidentiary balance, a lower threshold for initial market authorization will almost certainly equate to faster access to new drugs. The obvious danger of this is that potentially dangerous drugs may slip through the regulatory cracks, compromising patient safety.[78] Scholars, politicians, public interest groups, and media have argued that recasting the decision-making matrix for safety and efficacy in this manner will turn the public into guinea pigs for drugs that have not been adequately tested.[79] This position has been taken by Wright,[80] who claims that "regardless of the safeguards that are put in place, reducing the safety evidence required before new drugs are approved will make it very difficult to monitor and catch problems before it's too late." Indeed, there is significant evidence to suggest that post-market studies that have been recommended by regulators thus far are not usually conducted by sponsors once approval has been given.[81] If this scenario were to continue, it is not difficult to envision how the lifecycle approach would create an "evidence-free zone" for drug ap-

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74 See generally Murray Gell-Mann, *The Quark and the Jaguar: Adventures in the Simple and the Complex* (New York: W.H. Freeman and Company, 1994). The practical implications of elegance and symmetry in physics and mathematics are explored elegantly by Gell-Mann in the videocast. "Beauty and Truth in Physics" *TED TV VideoCast* (March 2007), online: TED Blog <http://blog.ted.com/2007/12/murray_gellmann.php>. But see Bruce Edmonds & Scott Moss, "From KISS to KIDS: An 'Anti-Simplistic' Modeling Approach" in Davidson et al., eds., *Multi-Agent and Multi-Based Simulation,* vol. 3415 (New York: Springer Berlin/Heidelberg, 2004) 130.

75 Bouchard, "Systems" and Bouchard, "Reflections", *supra* note 15. See also Wulf, *supra* note 15; David H. Guston, "Innovation Policy: Not Just Jumbo Shrimp" (2008) 454 Nature 940; Fred Gault & Sasanne Huttner, "A Cat's Cradle for Policy" (2008) 455 Nature 462.

76 For a detailed review of adaptive policy in a legal context, see J.B. Ruhl, "Regulation by Adaptive Management: Is It Possible?" (2005) 7 Minnessota Journal of Law Science & Technology 21 and references therein. See also Guston, *ibid.*

77 For a detailed review of robust policy-making in a political and international relations context, see: 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: SUNY Press, 2006).

78 *Supra* note 7.

79 Weeks, "Critics", *supra* note 8.

80 *Ibid.* See also 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) A7.

81 *Supra* note 9.

proval.[82] In the absence of reciprocal balancing by post-market surveillance, criticisms of this nature are well grounded in light of poor decisions by pharmaceutical firms to design, cover-up, or otherwise report clinical trial data selectively.[83]

Another significant question relating to PLF is the issue of flexible departure, concerns over which go well beyond the issue of faster approval times. These concerns flow from the fact that, under the terms of the proposed PLF regime, evidence of safety and efficacy in the context of flexible departure would be limited to reports of the most commonly-occurring adverse drug reactions,[84] presumably overlaid by the broader requirement for an "evidence-based" benefit-risk profile "favourable" to the drug.[85] Particular attention has been directed to the possibility that the standard for flexible departure under Bill C-51 (≥51% evidence of benefit-risk)[86] will lead to an industry-focused benefit-risk assessment framework.[87] Indeed, the issue of a shifted evidentiary framework has attracted consistent attention from commentators since GOC held its stakeholder workshops in 2006-2007, crystallizing with the announcement of Bill C-51 on April 8, 2008. Similar concerns have been expressed over provisions for accelerated[88] and conditional[89] approval in the U.S. and E.U.[90] Despite these criticisms, however, it is reasonable to speculate, based on policy documents published by Health Canada, the U.S. Institute of Medicine (IOM), the European Medicines Agency (EMEA), and FDA that the precautionary principle will not be replaced at the locus of the decision-making process in emerging lifecycle models. The "semi-quantitative" decision-making matrix elaborated by EMEA[91] in particular suggests that both objective and subjective metrics will be used as part of the benefit-risk analysis. This implies that a moderate articulation of the precautionary principle will be subsumed within benefit-risk calculations.[92]

Having said this, it remains true that an explicit ≥51% benefit-risk standard differs significantly from a soft or normative evidentiary standard of 85%, 75%, or even 65%. Indeed, one of the major implications of emphasizing faster access to innovative drugs is that enhanced access necessarily brings with it risks beyond those already present under the constraints of the existing clinical trial platform.[93] This is particularly true for drugs subject to early release to the public via flexible departure. Nevertheless, while drug agencies in Canada,[94] the U.S.[95], and the E.U.[96] have said that the risks of drug development must be shouldered by those that demand new and untested drugs, public opinion polls have clearly demonstrated that post-market safety should *not* be sacrificed for quick access to drugs. For example, in 2002, about the time that several high-profile safety withdrawals were coming to light and

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82 Edwin A.M. Gale, "Lessons from the Glitazones: A Story of Drug Development" (2001) 357 Lancet 1870.

83 *Supra* note 10. See also Trudo Lemmens, "Leopards in the Temple: Restoring Scientific Integrity to the Commercialized Research Scene" (2004) 32 J.L. Med. & Ethics 641; Trudo Lemmens, "Piercing the Veil of Corporate Secrecy about Clinical Trials" (2004) 34:5 Hastings Center Report 14.

84 Health Canada, "Concept Paper", *supra* note 50 at 19. For a more detailed discussion of the proposed evidentiary threshold under PLF, see Bouchard & Sawicka, *supra* note 2 at Section I.F(a) and Section II.

85 Weiss Smith, "Reply to Galson", *supra* note 11 at 2521.

86 *Bill C-51*, *supra* note 5 at cl. 8 ss. 18-19.

87 Hébert, *supra* note 7; Wayne Kondro, "Health Canada Proposes New Regulatory Regime for Drugs" (2007) 176 Canadian Medical Association Journal 1261.

88 FDA, "Fast Track", *supra* note 12.

89 *EMEA CHMP Guideline*, *supra* note 13.

90 For review, see Eichler, *supra* note 7 at 823.

91 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 1*]; 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 Authorization Applications of Medicinal Products for Human Use* (London: European Medicines Agency, 2008), online: EMEA <http://www.emea.europa.eu/pdfs/human/brmethods/1540407enfin.pdf> [*EMEA CHMP 2*].

92 For a discussion of the potential role of the precautionary principle in the PLF regime, see Bouchard & Sawicka, *supra* note 2 at Section I.C.

93 Eichler, *supra* note 7.

94 Peterson, "Innovation", *supra* note 6; Health Canada, "Blueprint", *supra* note 49.

95 *IOM Report*, *supra* note 9.

96 *EMEA CHMP 1* and *EMEA CHMP 2*, *supra* note 91; 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).

well before GOC's major policy articulations supporting PLF,[97] an exemplary study showed that two-thirds of the respondents indicated a preference to wait for "thorough safety testing" of new drugs, with two-fifths of the public stating that getting drugs approved "as fast as possible" is the "least important principle of the drug approval process … "[98] Regulators moving to embrace emerging lifecycle models would thus do well to heed the growing body of empirical studies on complex public health systems. Results from these investigations imply that in the absence of recognition of the dynamic nature of positive and negative feedback loops within the regulatory process, drug regulation has the potential to tilt precariously: first into subtle forms of policy resistance,[99] then into more obvious forms of policy failure,[100] and, potentially, into system collapse.[101] Given the persistence of serious, high-profile post-marketing safety controversies in the last decade, it could be speculated that the latter of these mechanisms presents the strongest stimulus for regulatory reform.

While the existing drug approval regime has raised many concerns over real or perceived conflicts of interest, it cannot be overlooked that GOC's PLF lifecycle initiative, as well as parallel initiatives by FDA and EMEA, is specifically intended to rectify some of these ills. Public perception of the intent behind these initiatives has not been helped by the previous "black box" nature of drug approval,[102] which is one of the dragons these agencies claim they want to slay.[103] As already noted, in various discussion and policy guidance documents, GOC, FDA, and EMEA all appear to be explicitly grappling with the inherent uncertainties, risks, and complexities of drug development. It is an obvious truism that this is not an easy path to walk and, as recognized by the major drug agencies in the U.S.[104] and Canada,[105] it will take active cooperation from the full range of public and private actors responsible for drug development, regulation, and consumption to make it work. As such, it is becoming increasingly accepted that the complexity, uncertainty, and risks of an rTPL innovation ecology in the medical sciences go hand in hand. They must be understood that way if we are to take the lessons learned from centuries of "linear" mental models and apply them to our growing understanding of complex "systems" models[106] like PLF which attempt to account for risk and uncertainty. There will be those who resist this evolution, but their numbers will eventually whittle away as empirical data challenge the simplistic assumptions underpinning the majority of linear models.[107]

In addition to offering a more realistic understanding of the risks and uncertainties involved in an rTPL ecology, there are other factors that render the lifecycle approach more advantageous than the existing regime. First, data on the correlation between user fee implementation and safety withdrawals

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97 Peterson, "Innovation", *supra* note 6; Health Canada, "Blueprint", *supra* note 49.

98 Commission on the Future of Health Care in Canada, *Public Input on the Future of Health Care: Results from the Issue/Survey Papers* (Ottawa: Pollara, 2002), online: Pollara <http://www.pollara.ca/Library/Reports/3461_pollara_english.pdf> (prepared by Pollara for the Commission). See also *Romanow*, *supra* note 68.

99 Bouchard, "Balancing", *supra* note 53; Lemmens & Bouchard, *supra* note 25. See also Sterman, "Reflections", *supra* note 52.

100 See generally Barry Bozeman, "Public Value Failure: When Efficient Markets May Not Do" (2002) 62 Pubic Administration Review 145; Barry Bozeman & Daniel Sarewitz, "Public Values and Public Failure in US Science Policy" (2005) 32 Science and Public Policy 119.

101 See generally Robert M. May, Simon A. Levin & George Sugihara, "Ecology for Bankers" (2008) 451 Nature 893. See also Per Bak & Maya Paczuski, "Complexity, Contingency, and Criticality" (1995) 92 Proceedings of the National Academy of Sciences 6689.

102 Ann Silversides, "Transparency and the Drug Approval Process at Health Canada" (2005), online: Woman and Health Protection <http://www.whp-apsf.ca/pdf/transparency.pdf> (citing (at 3) Abby Hoffman, head of Health Canada's Therapeutics Access Strategy, who made this comment in an address to the June 10, 2004 Health Canada public consultation).

103 Health Canada, "Blueprint", *supra* note 49; Health Canada, "Concept Paper", *supra* note 50; *Bill C-51*, *supra* note 5; Neil Yeates, David K. Lee & Maurica Maher, "Health Canada's Progressive Licensing Framework" (2007) 176 Canadian Medical Association Journal 1846.

104 *IOM Report*, *supra* note 9.

105 Peterson, "Innovation", *supra* note 6.

106 John H. Miller & Scott E. Page, *Complex Adaptive Systems: An Introduction to Computational Models of Social Life* (Princeton, NJ: Princeton University Press, 2007).

107 Sterman, "Reflections", *supra* note 52; Benoit Godin, "The Linear Model of Innovation: The Historical Construction of an Analytical Framework" (2006) 31 Science, Technology & Human Values 639 (it should be said however that Godin himself (at p. 35) referred to systems models of innovation as a "plate of spaghetti and meatballs").

are equivocal, even though data relating to the speed of review are not.[108] While some studies show a positive correlation, several detailed and statistically powered studies demonstrate a convincing lack of change in the pattern of withdrawals before and after user fees were implemented. Despite these differences, there appears to be significant acceleration in the incidence of serious adverse effects associated with withdrawals when they do happen, potentially due to the speed and breadth of market penetration and physician prescribing practices. Therefore, it would be desirable to have more studies on this issue in order to design a truly effective and efficacious lifecycle-based regulatory scheme. Moreover, as suggested by Carpenter *et al.*[109] and Olson,[110] even where it has been empirically demonstrated, an increase in post-user fee withdrawal rates may be due to the effects of reviewers working toward mandated deadlines rather than shorter review times per se. As noted by the authors, this situation could be rectified, at least in part, by devoting more resources toward staffing, including funds appropriated from parent public health agencies rather than via industry user fees.[111] Others have suggested curtailing direct-to-consumer advertising as a reasonable means to reduce accelerated market penetration and thus acceleration of the rate of adverse effects incidence.[112] As increasingly recognized by stakeholders in public debates and government-sponsored stakeholder workshops, it will be critical to educate the public as to the realities of information asymmetry and the principles of informed consent when requests are made for experimental therapies.

There is also the role of the physician-patient nexus to consider. Indeed, complexity theory posits that each actor is just as important as the next in producing positive, negative, and unintended outcomes in a complex system.[113] Even after the severity of recent drug withdrawal and conflict of interest controversies, society continues to be recalcitrant to lay blame on physicians, perhaps due to their "healing" function and fear of its withdrawal. Along these lines, individual members of the public can no longer claim to be passive receptacles of drugs they assume are safe and efficacious. Each actor in the rTPL ecology must accept accountability for their role in the failure of the linear model of drug innovation. The necessity of distributing accountability to include not just obvious targets such as firms and government, but also physicians and the public, was recognized by the IOM in its influential report on drug regulation.[114] Narrowing clinical trial populations to hit desired safety or efficacy signals for market authorization differs from the scope of drug-prescribing practices by physicians. Both types of practices have different sets of motivations and incentives.[115] Physicians, if they are to play a positive rather than a negative role in moving PLF forward, must be more cognizant and prudent in their prescribing habits regardless of demands on their time. One prospective outcome of the principle of unintended consequences is that even one physician prescribing a drug off-label,[116] no matter what his motives (selfish or altruistic), can contribute to a non-linear avalanche of similar prescribing practices.[117] Positive feedback loops such as those initiated by pharmaceutical advertising or patient advocacy groups may serve to speed this process exponentially. Support for this assumption comes from the apparent acceleration of mortality and morbidity associated with recent high-profile drug withdrawals as

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108 Bouchard & Sawicka, *supra* note 2 at Section I.B and Section I.E.

109 Carpenter, Zucker & Avorn, *supra* note 59.

110 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.

111 Daniel Carpenter *et al.*, "Approval Times for New Drugs: Does the Source of Funding for FDA Staff Matter?" (2003) W3 Health Affairs 618 at 623.

112 For review, see Lemmens & Bouchard, *supra* note 25.

113 *Miller & Page, supra* note 106; Sterman, "Reflections"*, supra* note 52; John D. Sterman, *Business Dynamics: Systems Thinking and Modeling for a Complex World* (Homewood, IL: Irwin/McGraw-Hill, 2000); James Gleick, *Chaos: Making a New Science* (New York: Penguin, 1988); M. Mitchell Waldrop, *Complexity: The Emerging Science at the Edge of Order and Chaos* (New York: Simon & Schuster, 1992); John L. Casti, *Complexification: Explaining a Paradoxical World Through the Science of Surprise* (New York: Harper Collins, 1994); Albert-Laszlo Barabasi, *Linked* (New York: Penguin Group, 2002).

114 *IOM Report*, *supra* note 9 (specifically, the IOM called on the FDA, industry, prescribing physicians, the health care delivery system, academic researchers, patients, and the general public to contribute to enhanced accountability of the drug regulatory system, underscoring (at S-4) that the "FDA's credibility is intertwined with that of the industry, and a more credible drug safety system is in everyone's best interest").

115 Lexchin, "Withdrawals", *supra* note 46 at 765.

116 Lemmens & Bouchard, *supra* note 25 at 335-337.

117 For description of how small events can give rise to large system-wide effects, see Bak & Paczuski, *supra* note 101.

well as the speed of drug agency withdrawals in response to this trend.[118] The FDA's rebuke[119] to "think it through" when managing benefits and risks applies equally well to patients and physicians. The relevance of this approach is underscored by the multiple layers of unknowns in the so-called "real world" use of drugs,[120] which, once understood, should countenance caution rather than innovation in prescribing and consuming practices.

It will of course be left to government as elected representatives to balance the range of competing public and private interests in the commercialization and regulation of publicly-funded medical research. Purposive legal-regulatory balancing is new neither to legal nor political communities, as is evident in the rich interplay between IPR rights and competition law as well as rights balancing in human rights, administrative, and constitutional law.[121] This body of jurisprudence suggests that the goals of society and those of individuals can be appropriately prioritized and balanced and that it is the role of law to do so. Interestingly, there is some evidence to suggest that the withdrawal rate due to post-marketing safety considerations is declining along with reductions in approvals involving New Active Substances/New Chemical Entities, even though the breadth of this submission classification in terms of chemical structure and indication is very wide. If borne out by further empirical research, these data suggest that as pharmaceutical firms increase their benefit-risk ratio and reduce the costs of developing therapeutic products, the benefit-risk profile and social costs of public drug consumption will change correspondingly.

D. Government as Representative Public Agent

The most important actor in the rTPL innovation ecology is government as the elected agent of the public. Balancing layer upon layer of public and private interests in GOC's proposed lifecycle model therefore requires strong, if not aggressive, government leadership in punishing breaches of post-market licence terms and conditions. Drug agencies, however, are not neutral actors. Rather, they are political actors that demonstrate their preferences through relevant networks of laws and regulations.[122] Of concern in this regard is the fact that the PLF framework enshrined in Bill C-51 contains a highly flexible multi-stage, multi-threshold process for suspension and revocation of clinical trial and market authorizations.[123] Such flexibility, combined with wide discretionary powers,[124] provides the legal grounds for GOC to take either a strong or lax approach to industry post-market compliance, notwithstanding new provisions directed to enforcement.[125] As discussed previously,[126] the question is an open one as to which position GOC will take.

It is not surprising that pharmaceutical firms, being self-interested actors, have complied poorly or not at all with their post-market obligations.[127] Despite claims that much of this has to do with a lack of

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118 Carpenter, Zucker & Avorn, *supra* note 59 at 1355.

119 U.S., Center for Drug Evaluation and Research (FDA), "Think It Through: A Guide to Managing the Benefits and Risks of Medicines", online: FDA <http://www.fda.gov/Drugs/ResourcesForYou/ucm079492.htm>. See also Sharon Smith Holston, "The Value of Patient's Perspective in FDA's Decision Process" (Presentation at 10th IMS International Symposium, Brussels, 3 November 1997), online: FDA <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/PatientInvolvement/ucm123864.htm>.

120 Health Canada, "Blueprint", *supra* note 49; Health Canada, "Concept Paper", *supra* note 50; EMEA, *CHMP 1* and EMEA, *CHMP 2*, *supra* note 91; *IOM Report*, *supra* note 9. For review of uncertainties in the context of balancing access and safety, see Eichler, *supra* note 7.

121 Ron A. Bouchard, "KSR v. Teleflex Part 1: Impact of U.S Supreme Court Patent Law on Canadian Intellectual Property and Regulatory Rights Landscape" (2007) 15 Health L.J. 221 [Bouchard, "Landscape"].

122 Christopher J. Bosso, *Pesticides and Politics: The Life Cycle of a Public Issue* (Pittsburgh, PA: University of Pittsburgh Press, 1987).

123 *Bill C-51*, *supra* note 5 at cl. 8 ss. 18-19.

124 *Ibid.* at cl. 8 ss. 15.1, 18.1-18.9, 19.1-19.9, 20.1-20.9, 21, 21.1-21.2, cl. 10 ss. 23.1-23.9, 24.1, and cl. 11 s. 30.

125 *Ibid.* at cl. 10 ss. 23 and 24.

126 Lemmens & Bouchard, *supra* note 25 at 365.

127 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> [Union]; David B. Ross, "The FDA and the Case of Ketek" (2007) 356 New Eng. J. Med. 1601. See also Susan Okie, "What Ails the FDA?" (2005) 352 New Eng. J. Med. 1063; Gardiner Harris, "FDA Scientists Accuse Agency Officials of Misconduct" *New York Times* (18 November 2008), A15 (describing a letter sent by FDA scientists on October 14, 2008 to Congress alleging FDA is engaged in "serious misconduct" by

jurisdiction by relevant drug agencies,[128] there is no question that these same agencies and pharmaceutical firms have pushed hard to locate common ground in their respective innovation and drug approval mandates. It is imperative, however, that governments maintain an arm's length relationship with industry if they are to embrace the regulatory norms of increased transparency and post-market safety[129] and to avoid charges of bias and unfairness in the discharge of their public health mandates. This will be hampered to the extent that (a) there is tension in the function of these agencies to stimulate the economy and protect the public and (b) when public health agencies do focus on the latter they are pushed by other governmental agencies and departments to focus on the former. Indeed, as noted by us[130] and others,[131] it is not just the Therapeutic Products Directorate (TPD) or the Health Products and Food Branch (HPFB) or even Health Canada that is fully responsible for drug regulation and approval. Since repeal of compulsory licensing in favour of the current linkage regulation regime in 1993,[132] the public health mandate of GOC relating to drug regulation has become increasingly bifurcated. For example, while Health Canada administers the *Food and Drugs Act* and *Regulations*, Industry Canada is responsible for administering both the *Patent Act*[133] and *NOC Regulations*,[134] which link drug approval to drug patenting.[135] Further, the Privy Council is responsible for setting the tone for domestic regulation/deregulation and the increasing scope of regulatory harmony with food and drug agencies in other jurisdictions. A parallel situation exists in the U.S. with the *Hatch-Waxman*[136] linkage regime tying patent protection under the U.S. *Patent Act*[137] to drug approval under the *Food, Drug, and Cosmetic Act*[138] via patent listings in the Orange Book.[139]

One need not even focus on interagency conflict, as this tension is very much alive and well within drug agencies themselves. As noted by Psaty[140] and Weiss Smith,[141] the basic criterion for drug approval is that its benefits outweighs its risks, yet FDA apparently views its "dilemma" (even after the IOM Report was issued) as weighing the trade-off between access and safety.[142] A similar situation exists in the E.U.[143] and Canada.[144] How this trade-off is parsed is now recognized to permeate all aspects of the regulatory decision-making process,[145] with particular consequences for the assessment of both the

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approving unsafe or ineffective medications); Carpenter, Zucker & Avorn, *supra* note 59.

128 Health Canada, "Blueprint", *supra* note 49; Health Canada, "Concept Paper", *supra* note 50; Yeates, Lee & Maher, *supra* note 103; *IOM Report, supra* note 9; 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), online: FDA <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108833.htm>. See also Psaty & Charo, *supra* note 9.

129 For a general discussion of the need for transparency in pre-market and post-market stages in the U.S., Canada, and the E.U., see *IOM Report*, *supra* note 9; Weiss Smith, "Sidelining", *supra* note 11; Psaty & Burke and Psaty & Charo, *supra* note 9; Health Canada, "Blueprint", *supra* note 49; Health Canada, "Concept Paper", *supra* note 50; Yeates, Lee & Maher, *supra* note 103; EMEA, "CHMP Guideline", *supra* note 13; *EMEA CHMP 2*, *supra* note 91.

130 Bouchard, "Balancing", *supra* note 53; Ron A. Bouchard & Trudo Lemmens, "Privatizing Biomedical Research—A 'Third Way'" (2008) 26 Nature Biotechnology 31 [Bouchard & Lemmens, "Third Way"].

131 Weiss Smith, "Sidelining", *supra* note 11 at 961; Janice Graham, "Smart Regulation: Will the Government's Strategy Work?" (2005) 173 Canadian Medical Association Journal 1469; Psaty & Burke, *supra* note 9.

132 Bouchard, "Test", and Bouchard, "Living", *supra* note 53; Bouchard, "Landscape", *supra* note 121. See also Hore, *supra* note 71.

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

134 *Patented Medicines (Notice of Compliance) Regulations*, S.O.R./93-133 [*NOC Regulations*].

135 Bouchard, "Test", *supra* note 53.

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

137 35 U.S.C. §§ 1-376 (2000).

138 21 U.S.C. §§ 301-399a (2004). See also *Food and Drugs,* 21 C.F.R. §§ 1-1499 (2003).

139 21 U.S.C. §§ 355(j)(7)(A) (2004). For detailed description, see Caffrey & Rotter, *supra* note 71.

140 Psaty & Charo, *supra* note 9 at 1919.

141 Weiss Smith, "Sidelining", *supra* note 11 at 961.

142 But see Galson, *supra* note 11.

143 Eichler, *supra* note 7.

144 Graham, *supra* note 131; Bouchard, "Balancing", *supra* note 53.

145 Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What To Do About It* (New York: Random House, 2004); Jerome P. Kassirer, *On the Take: How Medicine's Complicity with Big Business Can Endanger Your Health* (New York: Oxford University Press, 2005); John Abramson, *Overdo$ed America: The Broken Promise of American Medicine* (New York: Harper Collins, 2004); Jay S. Cohen, *Overdose: The Case Against the Drug Companies* (New York: Penguin, 2001); Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*

benefits and risks of new drugs[146] under circumstances where vital information is provided only by pharmaceutical sponsors. This tension has produced a clear push-pull dynamic concerning the traditional gate-keeping role of elected government in public health and its now established responsibility to enhance national productivity and prosperity via innovative medical research.[147] Governments fulfill this obligation, in part, through policies favouring strong IPR rights for marketed products, despite ample evidence that stacking IPR rights is not the path to greater therapeutic product development.[148]

Here and elsewhere we have provided theoretical,[149] and empirical qualitative[150] and quantitative[151] evidence to suggest that too much of a focus on closed IPR rights may stifle innovation in an open rTPL ecology. Emphasis on private IPR rights in a public health context leads naturally to questions relating to the efficiency and effectiveness of innovation from a truly societal perspective,[152] owing not least to the possibility that consumers are paying monopoly prices for drugs that may offer little or no improvement over existing therapeutic products.[153] Related to this concern is the possibility that core public values underpinning public health care, IPR rights seen to drive national innovation, and public lobbying efforts in support of enhanced access to novel drugs may be quietly, but importantly, evolving over time away from communitarian interests. The result is that traditional conflict of interest models may now be in the direct firing line of sophisticated corporate strategists and lobbying groups. A shift in societal values of this nature may be related to the apparently growing emphasis in developed nations on legal rights protecting personal autonomy and individual choice over those rights emphasizing government fiduciary obligations and other collective rights; a trend that may have co-evolved with the importance of the individual over the collective in everyday life more generally.[154]

A shift in public values of this nature may be reflected in the apparently autopoietic standardization of government-industry partnerships over time.[155] Geographic differences in the norms of these partnerships have been discussed by Wiktorowicz.[156] Under her gaze, Canada is seen as a "middle way" jurisdiction, between the U.S. and France, where substantial partnerships and co-dependencies exist side by side with some arm's length adversarialism between GOC and industry. Canadian policy development relating to drug development and drug regulation has been described as a form of clientele plu-

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(New York: Alfred A. Knopf, 2003); Ray Moynihan & Alan Cassels, *Selling Sickness: How the World's Biggest Pharmaceutical Companies Are Turning Us All Into Patients* (Vancouver: GreyStone Books, 2005).

146 Weiss Smith, "Sidelining", *supra* note 11.

147 Gordon Schiff, *Contested Ground: Public Purpose and Private Interest in the Regulation of Prescription Drugs* by Peter Davis (1998) 19 Journal of Public Health Policy 240; Derek Bok, *Universities in the Marketplace: The Commercialization of Higher Education* (New Jersey: Princeton University Press, 2003); Sheldon Krimsky, *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* (Lanham MD: Rowman & Littlefield, 2003); Janet Atkinson-Grosjean, *Public Science, Private Interests: Culture and Commerce in Canada's Networks of Centres of Excellence* (Toronto: University of Toronto Press, 2006).

148 Anita Varma & David Abraham, "DNA is Different: Legal Obviousness and the Balance Between Biotech Inventors and the Market" (1996) 9 Harvard J.L. & Tech. 53; Glynn S. Lunney Jr., "E-Obviousness" (2001) 7 Mich. Telecomm. & Tech. L. Rev. 363; Bouchard, "Test" and Bouchard, "Living", *supra* note 53.

149 Bouchard, "Systems", and Bouchard, "Reflections", *supra* note 15.

150 Bouchard, "Balancing", *supra* note 53; Bouchard, "Test", and Bouchard, "Living", *supra* note 53.

151 Bouchard & Sawicka, *supra* note 2.

152 For a discussion of the public policy implications of the terms "efficiency" and "effectiveness", see Janice Gross Stein, *The Cult of Efficiency*, rev. 2d ed. (Toronto: House of Anansi Press, 2001).

153 Lexchin, "IP Rights", *supra* note 62; "Drugs in 2001", *supra* note 63; *Patented Medicine Prices Review Board Annual Report*, *supra* note 62; Tim Hubbard & James Love, "A New Trade Framework for Global Healthcare R&D" (2004) 2:2 PLoS Biology 147; Hong *et al.*, *supra* note 64.

154 Stein, *supra* note 152; Joseph Heath, *The Efficient Society: Why Canada Is as close to Utopia as It Gets* (Toronto: Penguin, 2001); Amartya Sen, "Equality of What?" (Tanner Lecture on Human Values delivered at Stanford University, May 22, 1979), online: The Tanner Lectures on Human Values <http://www.tannerlectures.utah.edu/lectures/documents/sen80.pdf>.

155 Autopoiesis refers to the process of self creation and/or self organization (Gr. *auto—αυτό* for self- and *poiesis—ποίησις* for creation or production). The term underscores a fundamental interrelationship between the structure and function of a system, typical examples being living systems and biological cells. For a general discussion of the importance of interrelationships of actors in social and technological networks, see Bruno Latour, *Science in Action: How to Follow Scientists and Engineers through Society* (Cambridge, MA: Harvard University Press, 1987); Bruno Latour, *We Have Never Been Modern* (Cambridge, MA: Harvard University Press, 2007).

156 Mary E. Wiktorowicz, "Emergent Patterns in the Regulation of Pharmaceuticals: Institutions and Interests in the United States, Canada, Britain and France" (2003) 28 J. Health Pol. 615.

ralism,[157] where a narrow economic interest (e.g., multinational pharmaceutical) strongly informs governmental policy-making in order to "preserve and protect the structural basis of that interest." There can be no doubt that, based on a review of the *Blueprint*,[158] Concept Paper,[159] and Bill C-51,[160] and related disclosures by GOC,[161] clientele pluralism has strongly informed both the policy and legislation underpinning the nation's lifecycle approach to drug regulation. Enhanced regulatory partnering predictably raises the spectre of regulatory (or mission) creep.[162] Indeed, this scenario has been consistently acknowledged by drug agencies themselves[163] and is viewed by many to tilt the balance of power toward corporations and away from the public interest.[164] Global harmonization efforts favouring standardization of drug approval may thus trigger a further downward spiral in standard-setting.[165] This trend may, ironically, be enhanced rather than mitigated by a novel and untested regulatory mechanism.[166]

Gaps between regulatory science and the science of regulation represent a vital issue for emerging lifecycle models of drug regulation. This is particularly true of the Canadian PLF regime, given the scope of concerns expressed over flexible departure and the substantial degree of discretionary power retained by GOC in relation to suspension and revocation of clinical trials and marketing authorizations. Consequently, and for the purposes of maintaining a robust distributive balance of public and private interests in therapeutic drug development and regulation, drug agency leadership will somehow need to retain the political and normative power to "step away" from their industrial partners in order to enforce fundamental legal powers relating to post-market safety. These powers include revoking expedited or otherwise probationary market authorizations where it is in the public's best interests rather than the best interests of relevant government-industry partnerships.

SUMMARY & CONCLUSIONS

The data in this report suggest that concerns to the effect that PLF represents a new direction with regard to Canada's drug regulatory regime may be somewhat overstated. Indeed, our empirical analysis shows that the nation's existing approval mechanism may already be anticipating the lifecycle approach and that this anticipation is occurring in an accelerated fashion. For this reason, we propose that flexible departure does not represent a new direction in Canadian drug regulation. Patients are already gaining more rapid access to experimental drugs that have a critical need for significant evidence of safety (and potentially efficacy) after the drug has entered the marketplace. Indeed, between 2006 and 2008, 5-7% of all NOCs issued by Health Canada to brand name pharmaceutical firms met this requirement. Remarkably, the trend for Priority Review and NOC/*c* approvals has completely reversed in the last seven years, with NOC/*c* approvals now almost double that of Priority Review. To date, none of the drugs approved via these streams have been withdrawn for post-market

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157 *Ibid.*, citing (at 43) M.M. Atkinson & W.D. Coleman, "Corporatism and Liberal Policy" in A. Carson, ed., *Organized Interests and the State* (London: Sage, 1985).

158 Health Canada, "Blueprint", *supra* note 49.

159 Health Canada, "Concept Paper", *supra* note 50.

160 *Bill C-51*, *supra* note 5.

161 Health Canada, "Stakeholder Workshop", *supra* note 56; Peterson, "Innovation", *supra* note 6.

162 Michael M. E. Johns, Mark Barnes & Patrick S. Florencio, "Restoring Balance to Industry-Academia Relationships in an Era of Institutional Financial Conflicts of Interest" (2003) 289 Journal of the American Medical Association 741; Michele Boldrin & David K. Levine, "The Economics of Ideas and Intellectual Property" (2005) 102 Proceedings of the National Academy of Sciences of the United States of America 1252; Daniel P. Carpenter, "The Political Economy of FDA Drug Review: Processing, Politics, and Lessons for Policy" (2004) 23:1 Health Affairs 52; Stuart Macdonald, "When Means Become Ends: Considering the Impact of Patent Strategy on Innovation" (2004) 16 Information Economics and Policy 135; Wayne A. Ray & C. Michael Stein, "Reform of Drug Regulation—Beyond an Independent Drug-Safety Board" (2006) 354 New Eng. J. Med. 194.

163 Union, Okie, and Ross, *supra* note 127; Carpenter, Zucker & Avorn, *supra* note 109; Harris, *supra* note 127; John Abraham, "The Pharmaceutical Industry as a Political Player" (2002) 360 The Lancet 1498.

164 See generally both Bozeman, and Bozeman & Sarewitz, *supra* note 100.

165 P. Lurie & L.D. Sasich, "Safety of FDA-Approved Drugs" (1999) 282 Journal of the American Medical Association 2297; John Abraham & Tim Reed, "Trading Risks for Markets: The International Harmonization of Pharmaceuticals Regulation" (2001) 3 Health Risk & Society 113; Wiktorowicz, *supra* note 156.

166 M.H. Hoeflich & Karen Norheden Hoeflich, "Accelerating Science: A Problem for the Legal System" (1992) 60 University of Missouri-Kansas City Law Review 717.

safety reasons. Given that the available evidence suggests that very few of the post-marketing obligations recommended by regulators are actually met by pharmaceutical firms in other jurisdictions, it would appear that one side of the access-safety balance may be receiving more attention than the other from regulators. It is hoped that this gap, and the attendant ability of drug agencies to enforce post-market terms and conditions, will be remedied by the provisions of Bill C-51 (or future related legislation). In this regard, it is imperative that GOC demonstrates strong and sustained leadership in suspending or revoking clinical trial and market authorizations where firms do not meet their obligations. This would be particularly relevant under conditions where drugs gain early market access via flexible departure. If not, it is plausible that a leftward shift in the access-safety balance will lead to more rather than less post-market safety issues. Strong leadership will also be vital where the incidence of serious adverse effects escalates in a non-linear or otherwise strongly time-dependent manner.

The data further suggest that the Canadian system of pharmaceutical innovation may be "doing more with less." This conclusion applies equally to the rate and direction of innovative activity undertaken by brand name and generic firms. New or standard drug submissions have been flat while supplementary and generic submissions have increased substantially. Even NOCs for NAS and Me Too drugs declined when compared to NOCs directed to Line Extensions and new indications. Data presented in Figs. 1-10 imply that the Canadian pharmaceutical industry, as a whole, is focusing on prolonging market share and leveraging the utility of existing technologies rather than on the development of first-in-kind "breakthrough" products. As such, the data support the conclusion that technology appropriation is alive and well in Canada. An "incremental" approach to drug development of this nature is supported by innovation theory, which suggests that firms will only innovate in an area to the extent they capture all or most of the surplus from incentives they generate.[167] Even so, too much of a focus on incremental innovation propped up by entrenched IPR rights has the potential to downplay or minimize important discourse(s) relating to the social returns from innovation.[168]

Firms are obtaining increasingly more supplementary NOCs, more IPR rights per marketed product, and more control over pre-approval and post-approval processes with fewer pre-market evidentiary requirements, and thus lower costs of drug development; however it is not only the pharmaceutical industry that may be doing more with less. The public is clearly gaining more rapid access to experimental drugs aimed at addressing presumed unmet medical needs. In balancing this benefit, however, the public is also being asked to shoulder more risk with less evidence of pre-market safety and efficacy in the context of flexible departure. Moreover, individuals are being exposed to fewer truly breakthrough drugs while paying more for those whose market value is being propped up by strong IPR rights, although this is offset somewhat by the concomitant increase in the availability of generic products. Whether the public will have more post-market protection on the other side of the balance is an open question, as it cannot be predicted what style of leadership GOC will bring to bear on the issue.

Finally, regulators are experiencing perhaps the greatest challenges to both limbs of the access-safety balance. Indeed, owing to uncertainties regarding post-market compliance and enforcement, it is not clear at this point whether governments will gain more clarity from less focus on the pre-market approval process and more on the post-marketing stage. Certainly, the speed of the approval process has increased owing to user fee implementation, enhanced regulatory harmony with other jurisdictions, and increased cooperation with firms. Unclear however, is whether or not drug regulators will ultimately have a better overall drug safety record as they attempt to recalibrate tolerance of risk and uncertainty at pre-market and post-market approval stages. It is hoped that when implementing the lifecycle approach, public health agencies fully embrace the complexity and systems nature of the rTPL innovation ecology in which drug regulation is embedded.

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[167] Ganuza, *supra* note 65, citing (at 2) W.D. Nordhaus, *Invention, Growth, and Welfare: A Theoretical Treatment of Technological Change* (Cambridge MA: MIT Press, 1969).

[168] E. Richard Gold, "The Reach of Patent Law and Institutional Competence" (2004) 1 University of Ottawa Law & Technology Journal 263; Bouchard & Lemmens, "Third Way", *supra* note 130.

Taking an adaptive, learning-based approach to drug regulation has a number of advantages over historical linear models of drug development and regulation. First, it allows regulators to accept that there is no such thing as an "optimal" front-loaded policy. Second, it will help broaden agency capacity bandwidth, in turn allowing regulators to adopt a paternalistic, partnership, and adversarial stance in its bargaining scenarios as necessary and sufficient. This should allow a regulatory culture to grow organically in response to complex environmental signals and therefore to help avoid the pitfalls of the existing front-loaded regime. Finally, taking an approach that is both adaptive and distributive in nature may afford government an excellent opportunity to react swiftly in response to dynamically changing post-marketing safety signals in a manner that is in the best interests of the public rather than those of government-industry partnerships.