THE *PAS DE DEUX* OF PHARMACEUTICAL REGULATION AND INNOVATION: WHO'S LEADING WHOM?

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ABSTRACT

Global drug development and regulation is undergoing a substantial transition, including redefinition of the roles of public and private actors responsible for developing, regulating, and paying for therapeutic products. This shift has been accompanied by growing debate over the validity of the claim that an efficiently functioning global public health system requires acceptance of models of drug development that promote early access to therapeutic products in exchange for strong intellectual property rights. Without these rights, advocates claim pioneering drug development will not occur. Here, we challenge this view, arguing that recent regulatory efforts designed to encourage the development of new and innovative drugs through the provision of strong patent and "linkage" rights, which legally tie drug patenting and drug approval, have in fact had the opposite effect. We provide data to suggest that the pharmaceutical industry is leaning away from the development of new drugs and towards incremental changes in existing drugs as a result of firms locking in to discrete rights targets provided for by law.

TABLE OF CONTENTS

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INTRODUCTION

Global drug development is currently undergoing a substantial transition, including major redefinition of the responsibilities of those who develop, regulate and consume therapeutic products. This shift has been accompanied by growing debate over the validity of the claim that an efficiently functioning public health system requires acceptance of emerging lifecycle, or "real world," models of drug regulation that promote early access to innovative therapeutic products, enhanced post-market surveillance, and strong intellectual property and regulatory (IPR) rights. Indeed, IPR rights are assumed necessary for all stages of the therapeutic product lifecycle, including publicly funded medical research, university technology transfer, private research and development activities, regulatory submission, and now even the post-market stage. Advocates claim that without IPR rights pioneering drug development would not occur and that the public would be left without breakthrough remedies. The goal of the research discussed in the present Article is to investi-

gate this claim empirically and to assess how IPR rights might be used more effectively to encourage innovation in the medical sciences. In particular, we investigate whether regulatory incentives specifically intended to stimulate innovation in the pharmaceutical sector via IPR rights are producing such innovations.

The study is split into three sections. The first is an empirical investigation into the type of drugs approved by domestic Canadian regulators as regulatory incentives intended to stimulate innovation came into force. The primary goal of this study is to quantitatively analyze various types of "new" and "follow-on" drugs. A related, though smaller, component is to investigate trends for these drug types in the context of Canada's emerging lifecycle regulatory regime for drug approval, referred to as the "Progressive Licensing Framework."[1] Progressive licensing is currently enshrined in Bill C-51. Given its emphasis on promoting early access, enhanced post-market scrutiny, and strong IPR rights, progressive licensing offers an excellent opportunity to probe the relationship between drug approval, drug patenting, and innovation in an emerging drug regulation model.

The second is an empirical study of patents and patent litigation associated with the various types of drug approvals identified in the first section. The primary goal of this project is to show how government regulation shapes the domestic market for brand name and generic products. Particular attention is given to changes in patenting and litigation patterns before and after the establishment of the Canadian "linkage regulations" regime in 1993, referred to as the Patented Medicines (Notice of Compliance) Regulations (NOC Regulations).[2] Linkage regulations are critical to drug development, as they legally tie drug approval to drug patenting and litigation and thus represent a primary mechanism by which regulators promote drug development in exchange for IPR rights.

The third section is an analytical model of regulated pharmaceutical innovation, which focuses on the effectiveness of regulatory incentives intended to encourage innovation. Of particular interest is the synchronization of drug approval, patenting, and litigation data to the establishment of NOC

1. *See generally* HEALTH CANADA, BLUEPRINT FOR RENEWAL: TRANSFORMING CANADA'S APPROACH TO REGULATING HEALTH PRODUCTS AND FOOD (2006), *available at* http://www.hc-sc.gc.ca/ahc-asc/alt_formats/hpfb-dgpsa/pdf/hpfb-dgpsa/blueprint-plan-eng.pdf [hereinafter HEALTH CANADA, BLUEPRINT]; HEALTH CANADA, THE PROGRESSIVE LICENSING FRAMEWORK CONCEPT PAPER FOR DISCUSSION (2006), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfbdgpsa/pdf/prodpharma/proglic_hom prog_concept-eng.pdf [hereinafter HEALTH CANADA, PLF CONCEPT PAPER]; Neil Yeates et al., *Health Canada's Progressive Licensing Framework*, 176 CAN. MED. ASS'N J. 1845 (2007).

2. Patented Medicines (Notice of Compliance) Regulations SOR/1993-133 (Can.).

Regulations and progressive licensing. Given that progressive licensing is still being formally incorporated into the nation's regulatory regime, the majority of the analysis focuses on the relationship between drug approval, patenting, and litigation under the NOC Regulations.

I. BACKGROUND

A. PHARMACEUTICAL MARKET

Pharmaceutical products occupy an established and rapidly growing niche in modern health care. Estimated global pharmaceutical sales were U.S. $773 billion in 2008, up from $605 billion and only $298 billion in 2005 and 1998, respectively.[3] Sales growth has been strong in North America (12.6% per year from 1998 to 2005) compared to Europe (9.3%),[4] with the former accounting for the largest share of global sales (46%) compared to the latter (29.97%).[5] Even in a relatively small and growing market such as Canada,[6] more than 22,000 pharmaceutical products are currently available[7] and this number is growing rapidly.[8] Indeed, prescription drugs comprise the fastest rising component of domestic health care spending.[9] By 2006, drug expenditures in Canada rose to 17.4% of total health expenditures, up from 9.6% in 1985.[10]

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3. INTERCONTINENTAL MARKETING SERVICES HEALTH INC., GLOBAL PHARMACEUTICAL SALES, 2001–2008 (2008); INTERCONTINENTAL MARKETING SERVICES HEALTH INC., GLOBAL PHARMACEUTICAL SALES, 1998–2005 (2005). As noted by IMS, the "value of the global pharmaceutical market in 2010 is expected to grow 4–6 percent on a constant-dollar basis, exceeding $825 billion, driven by stronger near-term growth in the U.S. market" and "is expected to expand to $975+ billion by 2013." Gary Gatyas & Clive Savage, *IMS Forecasts Global Pharmaceutical Market Growth of 4 - 6% in 2010; Predicts 4 - 7% Expansion Through 2013*, INTERCONTINENTAL MARKETING SERVICES HEALTH CAN., OCT. 7, 2009.

4. OFFICE OF FAIR TRADING, ANNEX D: GLOBAL OVERVIEW OF THE PHARMACEUTICAL INDUSTRY 8 (2007).

5. MEDICINES AUSTRALIA, GLOBAL PHARMACEUTICAL INDUSTRY FACTS AND FIGURES 1 (2007).

6. *See* PATENTED MEDICINE PRICES REVIEW BOARD, ANNUAL REPORT 2008, at 37 (2009), *available at* http://www.pmprb-cepmb.gc.ca/cmfiles/PMPRB-AR08-E.pdf. Canada's share of drug sales in major markets increased from 2.4% in 2001 to 3.8% in 2008. More significantly, domestic growth in pharmaceutical sales was 7% from 2007 to 2008 compared with 2.7% in all major markets and 1% in the United States over the same time frame. *Id.*

7. HEALTH CAN., ACCESS TO THERAPEUTIC PRODUCTS: THE REGULATORY PROCESS IN CANADA 3 (2006), *available at* http://www.hc-sc.gc.ca/ahc-asc/alt_formats/hpfb-dgpsa/pdf/pubs/access-therapeutic_acces-therapeutique-eng.pdf.

8. CAN. INST. FOR HEALTH INFO., DRUG EXPENDITURE IN CANADA 1985 to 2008, at 6 (2009).

9. Trudo Lemmens & Ron A. Bouchard, *Regulation of Pharmaceuticals in Canada*, *in* CANADIAN HEALTH LAW AND POLICY 311, 312 (Jocelyn Downie et al. eds., 3rd ed. 2007).

10. CAN. INST. FOR HEALTH INFO., *supra* note 8, at 3. Total drug expenditures were CN $4 billion, $10 billion, and $18 billion in 1985, 1995, and 2002, increasing to $25.5 billion

Indeed, drug expenditures grew faster than all other expenses within the Canadian health care system, with an average growth rate of 9.4% between 1985 and 2006 compared with 6.6% for total health spending.[11] Similarly, per capita expenditures increased on average 8.2% per annum between 1985 and 2006, faster than France, Germany, Japan, Sweden, Finland, Norway, and other European nations.[12] Between June 2004 and June 2005 alone, a total of 378 million prescriptions were filled in Canada.[13] According to Organisation for Economic Co-operation and Development (OECD) data, Canada ranked third in the world in per capita drug expenditures by 2002, behind only the United States and France.[14] Drug sales with patent protection lead the way in pharmaceutical expenditures. Between 1990 and 2008, patented drug product sales in Canada increased 764%, from CN $1.7 billion to $13 billion per annum.[15] Global and domestic pharmaceutical markets therefore are entrenched and growing more rapidly than other health care segments.

B. DRUG APPROVAL

While drug products have become an essential element of domestic and global public health systems, concerns have nevertheless been raised about the willingness of the public to underwrite the cost of drugs that are extensions of already marketed products. Indeed, there has been considerable debate over the last 25 years relating to the social benefits of "new" drug products versus those referred to variously as "follow-on," "incremental," "line extension," "me too," and "supplemental" products. To this list one can add generic drugs that are bioequivalent to already marketed products. This is because all drug products that are not considered breakthrough or pioneering in nature represent by definition some form of technology appropriation, i.e., they come into being as a result of a party's ability to capture profits generated from their own or related inventions.[16] Many commentators have derided the social value of follow-on innovations.[17] Others, however, have claimed

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in 2006. Similarly, per capita expenditures were CN $150, $350 and $600 for the same fiscal years, increasing to $776 in 2006. *Id.* at 6–8.

11. *Id.* at 60–63.

12. *Id.* at 31.

13. INTERCONTINENTAL MARKETING SERVICES HEALTH, COMPUSCRIPT REPORT 2004, at 1 (2004).

14. ORG. FOR ECON. CO-OPERATION AND DEV., OECD HEALTH DATA 2004 (2004).

15. PATENTED MEDICINE PRICES REVIEW BOARD, *supra* note 6, at 23.

16. *See generally* David J. Teece, *Profiting from Technological Innovation: Implications for Integration, Collaboration, Licensing and Public Policy*, 15 RES. POL'Y 285 (1986).

17. *See, e.g.*, JAMES LOVE, CONSUMER PROJECT ON TECHNOLOGY, EVIDENCE REGARDING RESEARCH AND DEVELOPMENT INVESTMENTS IN INNOVATIVE AND NON-INNOVATIVE MEDICINES 20 (2003); Joel Lexchin, *Intellectual Property Rights and the Canadian*

that follow-on drugs represent a critical component of pharmaceutical industry innovation and that dire consequences will follow should policy-makers alter the current basket of legal and regulatory incentives for innovation.[18] An example of the tension between the utility of new and existing therapies is provided by the intensity of debate over Health Technology Assessment (HTA)[19] and Cost Effectiveness Research (CER),[20] particularly as it relates to the American Recovery and Reinvestment Act of 2009.[21]

1. Drug Approval Process and Terms

Given decades of effort towards global regulatory harmony, it is not surprising that the regulatory framework for drug approval in Canada parallels that of the U.S. Food & Drug Administration (FDA).[22] In both countries, drugs submitted through "New" or "Supplementary" pathways, can be classified as "First in Class," "Me Too," or "Line Extensions," under appropriate circumstances undergo some form of "expedited review," and can contain a "New Chemical Entity" (NCE) or "New Active Substance" (NAS). Typically, a sponsor files a New Drug Submission (NDS)[23] containing sufficient data on drug safety, efficacy, and quality to warrant approval (referred to as No-

Pharmaceutical Marketplace: Where do We Go from Here?, 35 INT'L. J. HEALTH SERV. 237, 243 (2005); *Drugs in 2001: A Number of Ruses Unveiled*, 11 PRESCRIRE INT'L 58, 58 (2002).

18. *See, e.g.*, Joshua Cohen & Kenneth Kaitin, *Follow-On Drugs and Indications: The Importance of Incremental Innovation to Medical Practice*, 15 AM. J. THERAPEUTICS 89, 91 (2008).

19. *See generally* Egon Jonsson, *Development of Health Technology Assessment in Europe*, 18 INT'L J. TECH. ASSESSMENT HEALTH CARE 171 (2002).

20. COMM. ON COMPARATIVE EFFECTIVENESS RES. PRIORITIZATION, INST. OF MED. OF THE NAT'L ACADS., INITIAL NATIONAL PRIORITIES FOR COMPARATIVE EFFECTIVENESS RESEARCH (2009); FED. COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS RES., U.S. DEPT. OF HEALTH & HUMAN SERVS., REPORT TO THE PRESIDENT AND THE CONGRESS (2009), http://www.hhs.gov/recovery/programs/cer/cerannualrpt.pdf; G. Caleb Alexander & Randall S. Stafford, *Does Comparative Effectiveness Have a Comparative Edge?*, 301 J. AM. MED. ASS'N 2488 (2009); Jerry Avorn, *Debate about Funding Comparative-Effectiveness Research*, 360 NEW ENG. J. MED. 1927 (2009); John K. Iglehart, *Prioritizing Comparative-Effectiveness Research—IOM Recommendations*, 361 NEW ENG. J. MED. 325 (2009); Peter Singer, *Why We Must Ration Health Care*, N.Y. TIMES MAG., July 15, 2009, at MM38; Hans-Georg Eichler et al., *Use of Cost-Effectiveness Analysis in Health-Care Resource Allocation Decision-Making: How Are Cost-Effectiveness Thresholds Expected to Emerge?*, 7 VALUE IN HEALTH 518 (2004).

21. American Recovery and Reinvestment Act of 2009, Pub. L. No. 111-5, 123 Stat. 115 (2009).

22. *See* Lemmens & Bouchard, *supra* note 9, at 321; *see generally* Patricia I. Carter, *Federal Regulation of Pharmaceuticals in the United States and Canada*, 21 LOY. L.A. INT'L & COMP. L. REV. 215 (1999).

23. Lemmens & Bouchard, *supra* note 9, at 325; *see also* Food and Drug Regulations, C.R.C., ch. 870, at § C.08.002(1)(a) (2009). The Food and Drug Regulations are propagated under the general authority of the Food and Drugs Act, R.S.C., ch. F-27 (1985).

tices of Compliance or NOCs).[24] A Supplemental New Drug Submission (SNDS) may be filed for changes to a drug already marketed by that sponsor.[25] These include amendments to dosage, strength, formulation, manufacture, labeling, route of administration, or indication.[26] Products associated with an SNDS are typically referred to as line extensions, referring to the fact that they are extensions of already marketed products.[27] Generic manufacturers submit an Abbreviated New Drug Submission (ANDS) to obtain an NOC requiring that generic drugs be pharmaceutically equivalent to the reference brand name product.[28] Generic sponsors may also submit Supplemental Abbreviated New Drug Submissions (SANDS) when changes are made to a drug already on market. Consequently, both brand name and generic firms can make "new" and "supplemental," or "follow on," submissions.

NOCs can be granted in an expedited fashion under domestic food and drug law in two ways.[29] One is through Priority Review, which refers to the fast-tracking of eligible drug candidates "intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases or conditions" with an "unmet medical need or for which a substantial improvement in the benefit/risk profile is demonstrated."[30] Evidentiary requirements for safety, efficacy, and quality parallel those for non-priority submissions; the main difference is an accelerated review time.[31] In the second path, sponsors may be granted an "NOC with conditions"

24. Food and Drug Regulations, C.R.C., ch. 870 § C.08.002(2) (2009); Lemmens & Bouchard, *supra* note 9, at 325; *see also* HEALTH CAN., THERAPEUTIC PRODUCTS PROGRAMME GUIDELINE: PREPARATION OF HUMAN NEW DRUG SUBMISSIONS (1991), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/prephum-eng.pdf.

25. Food and Drug Regulations, C.R.C., ch. 870 § C.08.003 (2009).

26. *Id.* at § C.08.003(2); *see also* Lemmens & Bouchard, *supra* note 9, at 326.

27. Lexchin, *supra* note 17, at 243; *see generally* Song Hee Hong et al., *Product-Line Extensions and Pricing Strategies of Brand Name Drugs Facing Patent Expiration*, 11 J. OF MANAGED CARE PHARMACY 746 (2005).

28. The term "bioequivalence" refers to the requirement that the generic product must be equivalent to the already marketed "reference product" with regard to chemistry, manufacturing, route of administration, use, and therapeutic and adverse systemic effects. *See also* Food and Drug Regulations, C.R.C., ch. 870, at §§ C.08.001.1, C.08.002.1(1) (defining and discussing "Canadian reference product" and "pharmaceutical equivalent").

29. *See generally* Ron A. Bouchard & Monika Sawicka, *The Mud and the Blood and the Beer: Canada's New Progressive Licensing Framework for Drug Approval*, 3 MCGILL J.L. & HEALTH 49, 58–59 (2009).

30. HEALTH CAN., GUIDANCE FOR INDUSTRY: PRIORITY REVIEW OF DRUG SUBMISSIONS 1–2, 4 (2009), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/priordr-eng.pdf.

31. Lemmens & Bouchard, *supra* note 9, at 328.

(NOC/c)[32] 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.[33] In addition to less onerous evidentiary requirements, the targeted review time for NOC/c approval is significantly accelerated compared to that for standard NDS review.[34] The main difference with Priority Review is that NOC/c licensure is granted on the condition that the sponsor will perform additional post-market studies to confirm alleged benefits and risks.

While the definitions of new and supplementary (NDS and SNDS) brand name submissions, standard and supplementary generic submissions (ANDS and SANDS), and pathways for expedited review (Priority Review and NOC/c) are relatively simple and straightforward, the definitions of First in Class and Me Too drugs are much less so.[35] In Canada, First in Class drugs are those that consist of either (a) a new family of active ingredient(s), also known as New Active Substance (NAS),[36] or (b) old active ingredient(s) used for the treatment of a new indication. A drug is First in Class if there is no other drug on the market that belongs to the same compound family that is used for the same indication.[37] Conversely, Me Too drugs are those that offer "important therapeutic options," but that may have little or no change to the benefit-risk profile.[38] Essentially, Me Too drugs are comparable to other drugs in terms of compound and indication.[39]

Previously referred to as a "New Chemical Entity,"[40] the definition of

32. NOC/c approvals are granted pursuant to § C.08.004(1), in compliance with the conditions of use stipulated in §§ C.08.002(1)(g), C.08.002(1)(h), C.08.006(2)(b), and C.05.006(2)(a) of the Food and Drug Regulations, C.R.C., ch. 870 (2009).

33. HEALTH PRODS. & FOOD BRANCH, HEALTH CAN., GUIDANCE DOCUMENT: NOTICE OF COMPLIANCE WITH CONDITIONS (NOC/C) (2007), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/noccg_accd-eng.pdf.

34. HEALTH CANADA, *supra* note 7, at 10–11.

35. *See* Monika Sawicka & Ron A. Bouchard, *Empirical Analysis of Canadian Drug Approval Data 2001-2008: Are pharmaceutical players "Doing More With Less"?*, 3 MCGILL J.L. & HEALTH 85, 97–114 (2009).

36. DRUGS DIRECTORATE, HEALTH CAN., POLICY ISSUES—NEW ACTIVE SUBSTANCE (1991), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/nas_nsa_pol-eng.pdf.

37. Letters between author, David K. Lee, Dir., Office of Legislative and Regulatory Modernization, Health Can., Dr. Maurica Maher, Senior Scientific Advisor, Progressive Licensing Project, Health Can., and Lesley Brumell, Supervisor, Submission and Info. Policy Div., Health Can. (April–July 2008) (on file with author) [hereinafter Health Canada Personal Communication].

38. *Id.*

39. *Id.*

40. *Id.*

NAS encompasses a wide range of chemically active substances, including (a) a chemical or biological substance that has not been previously approved for sale as a drug, (b) an isomer, derivative, or salt of a chemical substance that is already approved for sale as a drug but differs in safety and efficacy properties, or (c) a biological substance previously approved for sale as a drug that differs in molecular structure, nature of the source material, or manufacturing process.[41] The scope of regulatory approval based on an NAS is thus wide and forms the basis for NDS, SNDS, First in Class, and Me Too categories, depending on the chemical nature and use of the compound.

Drugs approved through NDS and SNDS routes can be classified as either First in Class or Me Too. For the NDS route, First in Class drugs are those that contain either an NAS or are directed to a new use (or indication), whereas NDS Me Too drugs neither contain a new ingredient nor are directed to a new use, but instead have an improved benefit-risk profile. For the traditional "line extension" SNDS route, relatively small changes to existing chemical structures such as salts or isomers may still yield First in Class or Me Too designations. The difference is that while both SNDS First in Class and Me Too drugs can cover new chemical forms,[42] only drugs directed to a new use may be deemed First in Class SNDSs.[43] Those that do not are deemed Me Too.[44] Because even a follow-on First in Class drug must be directed to a new use as opposed to just a new chemical form with altered benefit-risk, a higher level of innovation is typically ascribed to SNDS and SANDS First in Class drugs as opposed to Me Too drugs.[45] It is not surprising that drugs containing an NAS can be approved via the SNDS route given the broad overlap between SNDS (change in dosage, strength, formulation, manufacture, labeling, route of administration, or indication) and NAS (isomers, derivatives, or salts of existing drugs with differing safety and efficacy profiles and/or source material and manufacturing process) requirements.[46]

2. Lifecycle Model and IPR Rights

Emerging global drug policy places increasing importance on the need to

41. DRUGS DIRECTORATE, *supra* note 36; Health Can., Drugs and Health Products—NOC Database Terminology, *available at* http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/noc-acc/term_noc_acc-eng.php.

42. Health Canada Personal Communication, *supra* note 37.

43. *Id.*

44. *Id.*

45. For a comparison of Canadian and WHO Family of International Classifications (WHO-FIC) and Me Too classifications schemes, see Sawicka & Bouchard, *supra* note 35, at 108 (comparing Tables 2 and 5).

46. See *infra* Section III.A for discussion of the difference between Me Too and First in Class drugs particularly in regards to Figure 3b and Table 4.

adopt the principles of "lifecycle" regulation.[47] Lifecycle regulation of pharmaceuticals involves all relevant research and development, clinical trial studies, regulatory approval, market authorization, and normative post-market prescribing and use by physicians and the general population.[48] As Canadian regulators recognize, the unique aspect of lifecycle regulation is the recognition that valuable knowledge about a product is continuously accumulated over its lifecycle, especially with respect to data regarding benefit-risk analysis.[49] This progression has obvious ramifications for safety problems that arise after market penetration. The assumption is that as a drug's benefit-risk profile changes with time, so too should its approval status,[50] thus allowing for an opportunity for regulators to adapt to changing conditions over time.[51]

Canada is currently in the process of integrating the lifecycle approach into its regulatory regime.[52] Under the terms of the progressive licensing framework, plans regarding post-market studies, monitoring, safety surveillance, and risk management will be required when a sponsor files its submission.[53] The standard for initial market authorization is a positive or favorable benefit-risk profile, with maintenance of market authorization requiring a continuing favorable benefit-risk profile throughout the product's life span.[54] Canada is not alone in its efforts to legislate lifecycle approaches. Indeed, the FDA,[55] U.S. Institute of Medicine (IOM),[56] and European Medicines Agency

47. *See* Hans-Georg Eichler et al., *Balancing Early Market Access to New Drugs with the Need for Benefit/Risk Data: A Mounting Dilemma*, 7 NATURE REVS. DRUG DISCOVERY 818, 823–24 (2008).

48. HEALTH CANADA, BLUEPRINT, *supra* note 1, at 3.

49. *Id.* at 16.

50. *Id.* at 17.

51. *See id.* at 12.

52. *See* Bouchard & Sawicka, *supra* note 29, at 72–77.

53. HEALTH CANADA, PLF CONCEPT PAPER, *supra* note 1, at 5.

54. *Id.* at 17, 20.

55. CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMIN., CONCEPT PAPER: PREMARKETING RISK ASSESSMENT (Mar. 3, 2003) (draft, on file with the author); CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMIN., CONCEPT PAPER: RISK MANAGEMENT PROGRAMS (Mar. 3, 2003) (draft, on file with the author); CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMIN., CONCEPT PAPER: RISK ASSESSMENT OF OBSERVATIONAL DATA: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT (Mar. 3, 2003) (draft, on file with the author); FOOD AND DRUG ADMIN., U.S. DEP'T. HEALTH AND HUMAN SERVS., INNOVATION STAGNATION: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS (2004); Jeffery L. Fox, *FDA embraces risk-management approach*, 21 NATURE BIOTECH. 1120 (2003); *see also* Guidance on Drug Safety Information, 72 Fed. Reg. 10224 (Mar. 7, 2007).

56. BD. ON HEATH CARE SERVS., INST. OF MED. OF THE NAT'L ACADS., PATIENT SAFETY: ACHIEVING A NEW STANDARD OF CARE (Philip Aspden et al. eds., 2004). For ex-

(EMEA)[57] recognized early that drug safety was well served by lifecycle models, including articulating the need for regulating therapeutic products in light of "real world" drug use.

IPR rights remain a pivotal element of lifecycle models of drug regulation. In accordance with the terms of its National Pharmaceutical Strategy[58]

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ample,

> Reviewers in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) must weigh the information available about a drug's risk and benefit, make decisions in the context of scientific uncertainty, and integrate emerging information bearing on a drug's risk-benefit profile throughout the lifecycle of a drug, from drug discovery to the end of its useful life.

Id. at S-2. For a discussion of a comprehensive, rather than silo-based, response to errors in patient care, see also COMM. ON QUALITY OF HEALTH CARE IN AM., INST. OF MED. OF THE NAT'L ACADS., TO ERR IS HUMAN: BUILDING A SAFER HEALTH SYSTEM (Linda T. Kohn et al., 2000).

57. COMM. FOR MEDICINAL PRODS. FOR HUMAN USE, EUROPEAN MEDS. AGENCY, REPORT OF THE CHMP WORKING GROUP ON BENEFIT-RISK ASSESSMENT MODELS AND METHODS, EMEA/CHMP/15404/2007 (2007), *available at* http://www.emea.europa.eu/pdfs/human/brmethods/1540407en.pdf. The EMEA states,

> The current report describes the technical and scientific highlights of all these consultations, incorporates reflections and draws recommendations from the think-tank group. Areas for improvement in the operations of the EMEA and its scientific Committees include strengthening of both the informal and formal dialogue already in place, in order to ensure a continual exchange throughout the life-cycle of the products.

Id. at 6. For general discussion of "continuing and contextual" pre-market and post-market analysis of benefit-risk approach, see generally: COMM. FOR MEDICINAL PRODS. FOR HUMAN USE, EUROPEAN MEDS. AGENCY, 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, EMEA/509951/2006 (2006); COMM. FOR MEDICINAL PRODS. FOR HUMAN USE, EUROPEAN MEDS. AGENCY, REFLECTION PAPER ON BENEFIT-RISK ASSESSMENT METHODS IN THE CONTEXT OF THE EVALUATION OF MARKETING AUTHORISATION APPLICATIONS OF MEDICINAL PRODUCTS FOR HUMAN USE, EMEA/CHMP/15404/2007 (2008), *available at* http://www.emea.europa.eu/pdfs/human/brmethods/1540407enfin.pdf.

58. FED./PROVINCIAL/TERRITORIAL MINISTERIAL TASK FORCE ON THE NAT'L PHARMS. STRATEGY, NATIONAL PHARMACEUTICALS STRATEGY: PROGRESS REPORT (2006), *available at* http://www.hc-sc.gc.ca/hcs-sss/alt_formats/hpb-dgps/pdf/pubs/2006-nps-snpp/2006-nps-snpp-eng.pdf. Intellectual property rights and pharmaceutical innovation comprise three of the five "pillars" of the nation's pharmaceutical policy. According to the Government of Canada, the five "pillars" of federal pharmaceutical policy are the following: (1) intellectual property, (2) pharmaceutical research and development, (3) international trade policy, (4) health care, and (5) consumer protection. Barbara Oullet, Pharmaceutical Management and Price Control in Canada 7 (Mar. 31, 2006) (presentation to the North American Pharmaceutical Summit, on file with the Berkeley Technology Law Journal). The National Pharmaceutical Strategy states that "Governments recognize the crucial role the innovative

and Smart Regulations initiative,[59] the government of Canada sees itself as a leader in developing an innovative drug regulation platform and in providing unique regulatory incentives to the pharmaceutical industry.[60] In this capacity, Canadian regulators are acting in tandem with their American and European counterparts, all of which claim that therapeutic product development is crucial for national prosperity and productivity in the global marketplace.[61] The specific goals of the latest round of reform are to: (1) facilitate biomedical innovation; (2) create incentives for drug development when the market itself does not; (3) allow for earlier access to new drugs; (4) create an informed consumer; and (5) increase the threshold for post-market drug safety. The emphasis on providing IPR rights incentives to the industry in order to support innovation follows numerous reports from the government and its consultants over the last number of years on the growing productivity gap in Canada and the commercialization of novel therapeutic products emanating from publicly funded medical research.[62]

A cornerstone of Canadian domestic lifecycle regulation is NOC/c-type approval.[63] This refers to a recalibrated balance between faster access to nov-

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pharmaceutical industry plays in the development of breakthrough drugs and that intellectual property protection is key to encouraging and supporting innovation." NATIONAL PHARMACEUTICALS STRATEGY, at 39.

59. EXTERNAL ADVISORY COMM. ON SMART REGULATION, SMART REGULATION: A REGULATORY STRATEGY FOR CANADA (2004), *available at* http://dsp-psd.pwgsc.gc.ca/Collection/CP22-78-2004E.pdf.

60. *See* Robert Peterson, Dir. General, Therapeutic Products Directorate, Lecture to the Ottowa Regional Conference, Innovation in Drug Regulation: Canada as a Leader (Feb. 11, 2005).

61. *See* 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?*, 13 B.U. J. SCI. & TECH. L. 120, 158–64 (2007).

62. *See, e.g.*, EXPERT PANEL ON COMMERCIALIZATION, PEOPLE AND EXCELLENCE: THE HEART OF SUCCESSFUL COMMERCIALIZATION 6 (2006); BRIAN GUTHRIE & TREFOR MUNN-VENN, CONFERENCE BD. OF CAN., SIX QUICK HITS FOR CANADIAN COMMERCIALIZATION: LEADERS' ROUNDTABLE ON COMMERCIALIZATION 1 (2005). For an analogous discussion of the importance of industrial intellectual property incentives in national productivity and prosperity in the United States, see generally COUNCIL ON COMPETITIVENESS, INNOVATE AMERICA: NATIONAL INNOVATION INITIATIVE SUMMIT AND REPORT (2005).

63. *See* HEALTH CANADA, PLF CONCEPT PAPER, *supra* note 1, at 20. Health Canada states,

> In keeping with the proposed life-cycle approach, maintenance of market authorisation could require a continuing favourable benefit-risk profile for the authorised conditions of use throughout the product's lifespan. The favourable benefit-risk profile would be based on the same elements required for initial market authorisation with some possible additions, i.e., substantial evidence of efficacy, safety, and quality; substantial evidence

el remedies (termed "flexible departure") and enhanced post-market oversight of safety, efficacy, and benefit-risk, with the possibility of revocation of initial approval if the terms of initial approval are not met. Unlike Priority Review, continuing approval after initial regulatory approval is contingent upon whether pharmaceutical sponsors meet the terms and conditions assigned to the NOC/c.[64] At first glance, emphasis on NOC/c over Priority Review may seem inconsistent with the lifecycle approach. However, fast-tracking eligible NDSs and SNDSs via Priority Review results in faster approval without a change in the amount of scientific evidence required prior to market entry.[65] The process remains front-loaded in that it does not demand that sponsors conduct post-marketing studies as a means to maintain approval status. In comparison, the NOC/c mechanism demands that sponsors are subject to legal scrutiny beyond initial market authorization in exchange for faster approval. The process is considerably more back-loaded in this regard and thus is more consistent with the lifecycle approach. It is reasonable to conclude therefore that NOC/c approvals are an excellent proxy for lifecycle regulation compared with Priority Review or approval via conventional NDS and SNDS pathways.

While lifecycle models have several advantages over existing approval models,[66] concerns persist that releasing drugs into the market earlier may be misguided, given evidence that pharmaceutical firms typically do not meet conditions associated with approval once in the market in the absence of legislation compelling them to do so.[67] Moreover, concerns have been expressed

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> for a favourable overall benefit-risk profile regarding the product and evidence of other important benefit-risk considerations relating to the impact of market authorisation on external decision-makers.

Id. Health Canada then clarifies the balance between the uncertainties of drug development and the importance of bringing new drugs to market as fast as reasonably possible:

> When a manufacturer is considering departing from the baseline requirement for substantial evidence of efficacy and safety for initial market authorisation, a more flexible approach regarding the underlying efficacy and safety evidence is envisaged when there is a compelling reason. While the regulatory requirement for a favourable benefit-risk profile for the drug's use under the proposed conditions would remain, initial requirements for substantial evidence of efficacy and safety may be counterbalanced against other, important evidence concerning contextual benefit-risk considerations. For example, the potential benefits of bringing the drug to market are deemed to outweigh the relatively increased uncertainty regarding the safety and efficacy.

Id. at 20–21.

64. *See generally* sources cited *supra* note 1.

65. Health Canada Personal Communication, *supra* note 37.

66. *See generally* Eichler et al., *supra* note 47.

67. UNION OF CONCERNED SCIENTISTS, VOICES OF SCIENTISTS AT FDA:

over the reading-in of TRIPS-based provisions incorporating strong IPR rights,[68] and specific language contemplating incorporation into policy and regulations any relevant knowledge, documents, or information produced by industry and its trade organizations.[69] While it is reasonable to speculate that the goal of these provisions is to facilitate global regulatory harmony, there is some unease that practices such as these serve the nation's economic goals more than its public health mandate.[70] This interpretation is bolstered by statements from various branches of government.[71]

PROTECTING PUBLIC HEALTH DEPENDS ON INDEPENDENT SCIENCE 1 (2006), http://www.ucsusa.org/assets/documents/scientific_integrity/Voices_of_Federal_Scientists.pdf. The Union of Concerned Scientists stated,

> From 2005 to 2007, the Union of Concerned Scientists (UCS) conducted five surveys of federal scientists to evaluate how U.S. agencies use—and misuse—science to make policy decisions . . . The results reveal extensive political interference in federal science, with serious and wide-ranging consequences for our health, safety, and environment. This interference has weakened the federal scientific enterprise and impaired the ability of U.S. agencies to serve the public interest, with the potential for long-lasting harm to the federal scientific work force.

Id.; *see also* Daniel Carpenter et al., *Drug-Review Deadlines and Safety Problem*s, 358 NEW ENG. J. MED. 1354 (2008); David B. Ross, *The FDA and the Case of Ketek*, 356 NEW ENG. J. MED. 1601 (2007) (discussing the illustrative case of the drug Ketek); Gardiner Harris, *FDA Scientists Accuse Agency Officials of Misconduct*, N.Y. TIMES, Nov. 18, 2008, at A15 (describing a letter sent by the FDA scientists on October 14, 2008 to Congress alleging FDA is engaged in "serious misconduct" by approving unsafe or ineffective medications); Susan Okie, *What Ails the FDA?*, 352 NEW ENG. J. MED. 1063, 1065–66 (2005) .

68. Bill C-51, 2nd Sess. 39th Parl., cl. 11 § 30(3) (Can. 2008). This bill states,

> Without limiting or restricting the authority conferred by any other provisions of this Act for carrying into effect the purposes and provisions of this Act, the Governor in Council may make the regulations that the Governor in Council considers necessary for the purpose of implementing, in relation to drugs, Article 1711 of the North American Free Trade Agreement or paragraph 3 of Article 39 of the Agreement on Trade-related Aspects of Intellectual Property Rights set out in Annex 1C to the WTO Agreement.

Id.

69. *Id.* at cl. 11 § 30(7)(b).

70. Janice Graham, *Smart Regulation: Will the Government's Strategy Work?*, 173 CAN. MED. ASS'N J. 1469, 1469 (2005).

71. *See, e.g.*, HEALTH PRODS. AND FOOD BRANCH, HEALTH CAN., CLINICAL TRIALS REGULATORY REVIEW—STAKEHOLDER WORKSHOP 6 (2007), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ctrf_o_eccr_a_2007-03-26-eng.pdf [hereinafter HEALTH CANADA, STAKEHOLDER WORKSHOP]; HEALTH CANADA, BLUEPRINT, *supra* note 1, at 8–9; HEALTH CANADA, PLF CONCEPT PAPER, *supra* note 1, at 21; Reg Alcock, President, Treasury Bd., Speech Accompanying the Launch of the Government of Canada's Implementation Plan for Smart Regulation (Mar. 24, 2005) (transcript available at http://www.tbs-sct.gc.ca/media/ps-dp/2005/0324_e.asp); Peterson, *supra* note 60; *see also* Lemmens & Bouchard, *supra* note 9.

C. LINKAGE REGULATIONS

One of the most strongly contested aspects of pharmaceutical policy concerns the role of intellectual property and regulatory rights in providing economic incentives to firms and in shaping the agenda for basic medical research.[72] "Intellectual property rights" usually refers to traditional patent rights, while "regulatory rights" encompasses the growing cache of exclusivity periods (e.g., data, market, and pediatric) attached to drug-approval data. The combination of both is referred herein as "IPR rights."

A relatively new addition to the basket of IPR rights is a novel form of legal ordering referred to as "linkage regulations." So named because they tie patent protection for marketed pharmaceuticals to the drug approval process, linkage regulations enable brand name pharmaceutical firms to list as many patents as are deemed relevant to a marketed product on a patent register.[73] In Canada, this occurs under the aegis of the Patented Medicines (Notice of Compliance) Regulations.[74] Each patent must be demonstrated in litigation to be invalid or not infringed for generic market entry.

Linkage regulations are critical to the maintenance of monopoly pricing by brand name pharmaceutical firms as blockbuster drugs near the end of their conventional patent protection (patents on NCEs or NASs). This is because patents listed on the patent register effectively allow for a second "term" of patent protection, provided that patents are deemed relevant to the already marketed product. As such, linkage regulations represent a primary mechanism by which regulators promote drug development in exchange for private IPR rights.

Given the pivotal nature of the relevance requirement, it is not surprising that legislators and the courts have battled intensely over the issue. Early Federal Court of Appeal jurisprudence rejected the notion of a strict relevance requirement, opting instead for a broad statutory reading to the effect that patents need only be relevant to a medicine rather than the drug form specifically approved by regulators.[75] In other words, patents could be listed

72. David H. Guston, *Innovation Policy: Not Just a Jumbo Shrimp*, 454 NATURE 940 (2008).

73. 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?*, 6 CAN. J. L. TECH. 1, 1–27 (2007) [hereinafter Bouchard, *Scientific Research*]; Ron A. Bouchard, *Living Separate and Apart is Never Easy: Inventive Capacity of the PHOSITA as the Tie that Binds Obviousness and Inventiveness in Pharmaceutical Litigation*, 4 U. OTTAWA L. & TECH. J. 1 (2007), *available at* http://ssrn.com/abstract=958927 [hereinafter Bouchard, *PHOSITA*]; Edward Hore, *A Comparison of United States and Canadian Laws as They Affect Generic Pharmaceutical Market Entry*, 55 FOOD & DRUG L.J. 373 (2000).

74. Patented Medicines (Notice of Compliance) Regulations SOR/1993-133 (Can.).

75. Eli Lilly Can. Inc. v. Canada, [2003] F.C.A. 24, ¶ 32, 34–35 (Can.).

generally for a drug rather than against a specific drug submission. This made it comparatively easier for brand name firms to extend patent monopolies via linkage regulations. In 2006, amendments made to the NOC Regulations required listed patents to contain at least one claim to the medical ingredient, formulation, dosage form, or use for which approval was granted.[76] This was supported by the Supreme Court of Canada in *AstraZeneca*.[77] Shortly afterward, the Federal Court of Appeal reversed its position, holding that specific relevance is required between the patent sought to be listed and the drug submission against which it was listed.[78] The intense volleying back and forth between litigants, legislators, and the courts over the issue of relevance suggests that framing a system of pharmaceutical innovation around the nexus between continuing patenting activity on drugs that have already been approved and related drugs is a contentious model of innovative drug development contingent upon strong IPR rights.

Prior to the NOC Regulations coming into force, the Supreme Court of Canada noted that patent protection and regulatory approval of pharmaceuticals were governed by different statutes as well as different policy goals and objectives. Given the specific language employed,[79] it is reasonable to con-

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76. Patented Medicines (Notice of Compliance) Regulations SOR/1993-133 (Can.).

77. AstraZeneca Canada v. Can. Inc., [2006] 2 S.C.R. 560, ¶ 21–23 (Can.) The court stated,

> I emphasize the words in s. 4(5) that in the case of patents added afterwards, "the first person must identify the submission to which the patent list or the amendment relates, including the date on which the submission was filed". In addition, s. 3(3) provides that "[n]o information submitted pursuant to section 4 shall be included on the register until after the issuance of the notice of compliance in respect of which the information was submitted." These provisions, it seems to me, provide an important key to understanding the scheme. Entry of the "Patent list" does not destroy the linkage between the patent and the submission(s) to which it relates, nor to the NOC to which the submission(s) are directed. Specific patents are associated with one or more NDS, ANDS or SNDS, which in turn (if approved) give rise to specific NOCs, which in turn approve a specific manufacturer's product, which a generic manufacturer may seek to copy.).

Id. at ¶ 21.

78. Wyeth Can. v. Ratiopharm, Inc., [2008] 1 F.C. 447, ¶ 30 (Can).

79. AstraZeneca Can. Inc. v. Canada, [2006] 2 S.C.R. 560, ¶ 12 (Can.). The court noted that

> [t]he *NOC Regulations* lie at the intersection of two regulatory systems *with sometimes conflicting objectives*. First, is the law governing approval of new drugs, which seeks to ensure the safety and efficacy of new medications before they can be put on the market. The governing rules are set out in the *Food and Drugs Act*, R.S.C. 1985, c. F-27 (*FDA*) and the *Food and Drug Regulations*, C.R.C. 1978, c. 870. The *FDA* process culminates (if success-

clude that the court was referring to the previously divergent goals of public health policy and industrial/economic policy. The language employed by the court further suggests that these two policy branches have formally converged in the form of the NOC Regulations and that private IPR rights are viewed as a primary driver of this convergence. Indeed, government Regulatory Impact Analysis Statements (RIAS) have forged a clear policy objective of stimulating innovation in the pharmaceutical sector predicated on industrial IPR rights, including via linkage regulations.[80]

The Canadian NOC Regulations were modeled after the U.S. Hatch Waxman linkage regime,[81] which ties patent protection under the Patent Act[82] to drug approval under the Food, Drug & Cosmetic Act[83] via patent listings in the Orange Book.[84] While the United States and Canada are currently the only two jurisdictions formally employing linkage regulations to stimulate innovation, there is movement afoot to institute linkage regulation regimes in other jurisdictions, and the United States is moving toward including linkage provisions in its international trade agreements.[85] Parallel developments have

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> ful) in the issuance of a NOC to an applicant manufacturer by the Minister of Health on the advice of his officials in the Therapeutic Products Directorate. The *FDA* objective is to encourage bringing safe and effective medicines to market to advance the nation's health. The achievement of this objective is tempered by a second and to some extent overlapping regulatory system created by the *Patent Act*, R.S.C., 1985, c. P-4. Under that system, in exchange for disclosure to the public of an invention, including the invention of a medication, the innovator is given the exclusive right to its exploitation for a period of 20 years. *Until 1993, the two regulatory systems were largely kept distinct and separate.*

Id. (emphasis added).

80. Bouchard, *supra* note 61, at 123; Bouchard, *PHOSITA*, *supra* note 73, at 46–51.

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

82. Patent Act, 35 U.S.C. §§ 1–376. (2006).

83. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j)(7)(A) (2006).

84. 21 U.S.C. § 355(j)(7)(A) (establishing a list of "Approved Drug Products with Therapeutic Equivalence" commonly known as the "Orange Book"); *see also* Andrew A. Caffrey, III & Jonathan M. Rotter, *Consumer Protection, Patents and Procedure: Generic Drug Market Entry and the Need to Reform the Hatch-Waxman Act*, 9 VA. J.L. & TECH. 1, 4–7 (2004) (describing the Orange Book in the context of patent litigation and drug development); Rebecca S. Eisenberg, *Patents, Product Exclusivity, and Information Dissemination: How Law Directs Biopharmaceutical Research and Development*, 72 FORDHAM L. REV. 477, 483 (2003) ("Holders of approved NDAs are required to disclose all patents that they believe would be infringed by unauthorized sales of the approved drug, and the FDA publishes the list in a publication called the Orange Book.").

85. *See, e.g.*, Judit Rius Sanjuan, *Patent-Registration Linkage*, CPTECH, Apr. 3, 2006, http://www.cptech.org/publications/CPTechDPNo2Linkage.pdf.

also taken place in other segments of the medical product development landscape. For example, both the United States National Institutes of Health (NIH) and Canadian Institutes for Health Research (CIHR) have stated that strong industrial and economic rights for biomedical firms are a fundamental linchpin for governments to fulfill their public health mandates.[86] Further evidence for convergence of domestic public health and economic policy is provided by the fact that although drug approval and drug policy have historically been controlled by Health Canada, drug patenting, drug approval-linkage, and innovation policy have become increasingly under the control of Industry Canada—setting up potential tension between the two branches of government.[87] A similar "push-pull" between public health and economic concerns is found in legislation and policy that underpins publicly funded medical research, technology transfer, and related commercialization activities in the United States and Canada.[88]

The specific platform of legal rights associated with pharmaceutical products has critical public health ramifications, not only because firms and policy-makers view it as a major economic driver for innovation in the life sciences,[89] but also because the rate and direction of innovation in the phar-

86. *See, e.g.*, EUROPEAN MEDS. AGENCY, THE EUROPEAN MEDICINES AGENCY ROAD MAP TO 2010: PREPARING THE GROUND FOR THE FUTURE, EMEA/H/34163/03/Final (2005) [hereinafter EMEA ROAD MAP]; U.S. DEPT. OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., INNOVATION OR STAGNATION: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS (2004); Alan Bernstein, *Toward Effective Canadian Public-Private Partnerships in Health Research*, 168 CAN. MED. ASS'N J. 288 (2003); Eichler et al., *supra* note 47, at 819; Elias Zerhouni, *The NIH Roadmap*, 302 SCI. 63 (2003). For example, the EMEA ROAD MAP stipulates that the agency uses a "two-pillar approach" to make safe and effective therapeutic products available to the public. EMEA ROAD MAP, at 36. These are to facilitate more rapid access to safe and effective medicines via amendment to the existing regulatory licensing framework and to facilitate industrial innovation. While EMEA does not provide a definition of "innovation" nor a "map" of how it will facilitate innovative drug development in either its road map or its follow-up report, it can be plausibly assumed that the main economic drivers for this process will be a combination of intellectual property and regulatory rights. EUROPEAN MEDICINES AGENCY, SECOND STATUS REPORT ON THE IMPLEMENTATION OF THE EMEA ROAD MAP, EMEA/359050/2007 (2007). Eichler et al. point out that "regulators acknowledge the need to facilitate innovation and the fact that a lack of efficacious therapies *is a public health issue*." Eichler et al, *supra* note 47, at 819 (citing EMEA ROAD MAP) (emphasis added).

87. *See generally* Ron A. Bouchard & Trudo Lemmens, *Privatizing Biomedical Research—a Third Way*, 26 NATURE BIOTECHNOLOGY 31 (2008) (examining the tension between for-profit entities and the public interest in biomedical research); Bouchard, *supra* note 61.

88. For discussion of the tension between public and private interests in publicly funded medical research, see Bouchard, *supra* note 61; *see also* SHELDON KRIMSKY, SCIENCE IN THE PRIVATE INTEREST (2003).

89. *See* CANADA'S RESEARCH-BASED PHARMACEUTICAL COMPANIES (RX&D), INFORMATION GUIDE 2002, SECTION 2: INDUSTRY ISSUES (2002), *available at*

maceutical industry may be shaped *antecedently* by IPR rights incentives.

D. IPR RIGHTS AND INNOVATION POLICY

IPR rights and public policy promoting innovation have strong historical associations. Public policy in most developed nations still tends to assume basically a linear model of innovation, i.e., a product "pipeline" that begins in basic research, moves on through private research and development activities, and then to commercialization in the form of products and services.[90] This model implies a strong imperative to legally protect knowledge that has been reduced to practice as it flows through the system in the form of limited-term monopolies. For pharmaceutical innovation, the process is complicated by regulatory requirements to gain market authorization for new drugs, which is perceived as the terminus for the innovation pipeline. Accordingly, there is a considerable body of established science policy that identifies IPR rights as the major economic driver of innovation, national productivity, and translational research in the medical sciences.[91]

Despite its entrenched nature, however, the theoretical and empirical case for linear models of innovation contingent on strong IPR rights is weak. Since the 1960s, much scholarly work on innovation has indicated a highly complex, iterative process of individual and organizational learning that typi-

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http://www.canadapharma.org/Industry_Publications/Information_Guide/section2_e.html; *see also* ASTRAZENECA CAN., THE PATENT ACT & LINKAGE REGULATIONS: ESSENTIAL TOOLS FOR THE ADVANCEMENT OF MEDICAL SCIENCE IN CANADA (2009), http://www.astrazeneca.ca/documents/en/aboutus/PatentActLinkageRegulations.pdf.

90. *See* Bouchard & Lemmens, *supra* note 87, at 35; *see generally* VANNEVAR BUSH, SCIENCE: THE ENDLESS FRONTIER (1945); DONALD STOKES, PASTEUR'S QUADRANT (1997); Benoît Godin, *The Linear Model of Innovation: The Historical Construction of an Analytical Framework*, 31 SCI. TECH. HUM. VALUES 639 (2006).

91. In its "Roadmap for Medical Research," the U.S. National Institutes of Health (NIH) defines "translational research" as research that successfully makes the transition translated from the laboratory bench to the patient bedside: "To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin at 'the bench' with basic research—in which scientists study disease at a molecular or cellular level—then progress to the clinical level, or the patient's 'bedside.'" NIH Roadmap for Medical Research, http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp (last visited Nov. 6, 2009). Similarly, the Canadian Institutes for Health Research (CIHR) has embedded the concept of "knowledge translation" into its statutory mandate: "The objective of the CIHR is to excel, according to internationally accepted standards of scientific excellence, in the creation of new knowledge and its translation into improved health for Canadians, more effective health services and products and a strengthened Canadian health care system." Canadian Institutes of Health Research Act § A, 2000 S.C., ch. 6 (Can.). For discussion of research in the specific context of commercialization of publically funded medical research, see generally Bouchard, *supra* note 61; KRIMSKY *supra* note 88; EXPERT PANEL ON COMMERCIALIZATION, *supra* note 62; GUTHRIE & MUNN-VENN, *supra* note 62; THE COUNCIL ON COMPETITIVENESS, *supra* note 62.

cally involves an array of public and private sector inputs with many feedbacks.[92] This body of work suggests that innovation is a dynamic combinatory process in which the probability of innovation is linked closely to the capacity to create new combinations of knowledge, resources, and skills.[93] Other empirical studies have failed to demonstrate a conclusive link between strong IPR rights policies and generally increased levels of innovation.[94] These studies suggest that the dynamics of innovation can embrace IPR rights in some circumstances, but that these rights need not comprise an essential element for innovation to occur or to increase. The implications of this scenario are especially important for innovative product development in the medical sciences, given the vast array of public health and cost considerations involved in new drug development and regulation.[95]

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92. *See, e.g.*, HENRY CHESBROUGH, OPEN INNOVATION: THE NEW IMPERATIVE FOR CREATING AND PROFITING FROM TECHNOLOGY (2003); DOMINIQUE FORAY, THE ECONOMICS OF KNOWLEDGE (2004); RICHARD NELSON & SYDNEY WINTER, AN EVOLUTIONARY THEORY OF ECONOMIC CHANGE 27–29, 277 (1982); W. Brian Arthur, *Competing Technologies, Increasing Returns, and Lock-in by Historical Events*, 99 ECON. J. 116 (1989); Wesley M. Cohen & Daniel A. Levinthal, *Absorptive Capacity: A New Perspective on Learning and Innovation*, 35 ADMIN. SCI. Q. 128 (1990); Giovanni Dosi, *Technological Paradigms and Technological Trajectories: A Suggested Interpretation of the Determinants and Directions of Technical Change*, 11 RES. POL'Y 147, 157–58 (1982); Henry Etzkowitz & Loet Leydesdorff, *The Dynamics of Innovation: From National Systems and "Mode 2" to a Triple Helix of University–Industry–Government relations*, 29 RES. POL'Y 109 (2000); Paul Nightingale, *A Cognitive Model of Innovation*, 27 RES. POL'Y 689 (1998).

93. COHEN & LEVINTHAL, *supra* note 92; W. Brian Arthur, *The Structure of Invention*, 36 RES. POL'Y 274 (2007); ERIC VON HIPPEL, DEMOCRATIZING INNOVATION (2005); C. Freeman, *Technological Infrastructure and International Competitiveness*, 13 INDUS. & CORP. CHANGE 541 (2004).

94. David C. Mowery et al., *The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980*, 30 RES. POL'Y 99 (2001); Mariko Sakakibara & Lee Branstetter, *Do Stronger Patents Induce More Innovation? Evidence from the 1988 Japanese Patent Law Reforms*, 32 RAND J. ECON. 77 (2001); Adam B. Jaffe, *The U.S. Patent System in Transition: Policy Innovation and the Innovation Process*, 29 RES. POL'Y 531 (2000); Roberto Mazzoleni & Richard R. Nelson, *The Benefits and Costs of Strong Patent Protection: A Contribution to the Current Debate*, 27 RES. POL'Y 273 (1998). For a recent review of empirical studies, see JAMES BESSEN AND MICHAEL J. MEURER, PATENT FAILURE (2008).

95. *See* Comm'n of Patents v. Fabwerka Hoechst, [1964] S.C.R. 49, 56 (Can.). In emphasizing that courts must scrutinize pharmaceutical patents carefully in order to determine if they properly merit the grant of a monopoly privilege in light of the significant public interest at stake, the court noted that

> [i]n the particular class of case with which we are here concerned dealing with drugs and medicines, there is considerable public interest at stake, and the Commissioner should most carefully scrutinize the application to see if it merits the grant of monopoly privileges, and to determine the scope of the monopoly available.

Id.; *see generally* Catherine De Angelis et al., *Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors*, 351 NEW ENG. J. MED. 1250 (2004).

In light of the increasing disparity between the claim that an effective and efficiently operating public health system is contingent upon IPR rights[96] and the evidence disputing the legitimacy of this model,[97] therapeutic product development represents an excellent target for empirical studies of the relationship between legal incentives for innovation and product development. As noted by Jaffe, robust conclusions regarding the consequences for technological innovation of changes in patent policy are few and far between, in large part owing to a fundamental lack of empirical data.[98] The combination of recently established linkage and lifecycle regulation based models of drug de-

96. *See, e.g.*, Bouchard & Sawicka, *supra* note 29, at 65 n.168; Eichler et al., *supra* note 47.

97. *See, e.g.*, Jaffe, *supra* note 94; Mazzoleni & Nelson, *supra* note 94; Keith Pavitt, *National Policies for Technical Change: Where are the Increasing Returns to Economic Research?*, 93 PROC. NAT'L ACAD. SCI. U.S.A. 126 (1996); *see generally* MICHELE BOLDRIN & DAVID K. LEVINE, AGAINST INTELLECTUAL MONOPOLY (2008); KRIMSKY, *supra* note 88.

98. Jaffe, *supra* note 94. Jaffe notes that it is possible that the R&D boom in the late 1970s and early 1980s would not have been so large or lasted so long without enhanced IPR rights, and that it is "disquieting, however, that there is so little empirical evidence that what is widely perceived to be a significant strengthening of intellectual property protection had significant impact on the innovation process." *Id.* Jaffe further observes,

> Overall, there is a noticeable gap between the highly developed theoretical literature on patent scope and the limited empirical literature. This is due partially to the infrequency of changes in patent regimes like the one examined by Sakakibara and Branstetter. Part of the difficulty also lies in the weakness of the connection between the model constructs and quantifiable aspects of a patent regime.

Id. at 588. Finally, Jaffe comments that

> [t]his limited success is due partially to the difficulty of measuring the parameters of patent policy, and partly due to the difficulty of discerning statistically significant effects when many things have been changing at the same time. But it should surely be viewed as a challenge to researchers to try to do more.

Id. at 554. Similar conclusions were drawn by Mazzolini and Nelson and more recently by Boldrin and Levine. Mazzoleni & Nelson, *supra* note 94. Mazzolini and Nelson stated,

> The range of arguments about the positive social value of patents is obviously much wider than the area of strong empirical studies explored to date. An analyst, citing earlier studies that appear to show limited value, obviously is vulnerable to the argument that those studies do not provide evidence on some of the possibly most important functions patents serve. We cannot present here an empirically supported and intellectually persuasive argument on this broad question. The important empirical research that needs to be done in order to map out the basic facts simply has not been done yet.

Id. Boldrin & Levine, *supra* note 97, at 189–90. In a meta-analysis of empirical studies of whether introducing or strengthening patent protection leads to greater innovation, Boldrin and Levine note: "We have identified twenty three economic studies that have examined this issue empirically. The executive summary: these studies find weak or no evidence that strengthening patent regimes increases innovation; they find evidence that strengthening the patent regime increases . . . patenting!" *Id.* at 216–17; *see also* Pavitt, *supra* note 97, at 126.

velopment, therefore, provide a unique and time-sensitive opportunity to develop a domestically based yet globally relevant methodology and database for the study of pharmaceutical innovation.

Considerations, such as the aforementioned, led to the current study. Our ultimate goal is to develop an independent empirical methodology to identify patterns in the rate and direction of innovative activity by pharmaceutical firms and to analyze these data in relation to well defined regulatory incentives for pharmaceutical innovation via provision of strong IPR rights. The work is specifically designed to probe the functional and structural link between drug approval, drug patenting, drug litigation, and pharmaceutical innovation. Here, we present data from our study on the relationship between drug approval, drug regulation, and drug innovation in the domestic Canadian market. We analyzed drug approvals over the period 2001–2008, with a particular focus on the types of drugs being approved and how approvals were consistent with emerging lifecycle models of drug regulation.[99] The second major aspect of the work is a pilot study on the legal nexus between drug approval, drug patenting, and litigation, which we propose reflects trends in the broader influence of government regulation on innovation in the global pharmaceutical industry. Specifically, we argue that the global pharmaceutical industry is leaning away from the development of new drugs and towards incremental changes in existing drugs as a result of firms locking in to discrete IPR rights targets provided for by law.

II. METHODS

A. DRUG APPROVAL

Statistical analysis of drug approvals issued in Canada from January 1, 2001 to December 31, 2008 was performed as described previously.[100] Absolute numbers and fractional percentages of various types of drug approvals were calculated for each year during the eight-year test period in annual, quarterly, monthly and daily increments. Drug approvals used for calculation include NDS, SNDS, ANDS, SANDS submissions, those directed to an NAS, First in Class drugs, Me Too drugs, and drugs approved via the two expedited review streams (Priority Review and NOC/c).

For the present purposes, "new" drugs were those that were either approved through the New Drug Submission (NDS) stream, contained a New Active Substance (NAS), or directed to First in Class (FIC) drugs. In con-

99. For discussion of lifecycle drugs, see generally Eichler et al., *supra* note 47; Yeates, et al., *supra* note 1.

100. *See* Sawicka & Bouchard, *supra* note 35, at 92.

trast, "follow-on" drugs were either brand name drugs approved through the Supplementary New Drug Submission (SNDS) stream, approved via the SNDS stream directed to FIC therapies, approved via the SNDS stream containing an NAS, or generic drugs approved via either the standard Abbreviated New Drug Submissions (ANDS) stream or the follow-on Supplementary ANDS (SANDS) stream. The classification system is summarized for convenience in Table 1.

Table 1: Classification Scheme for New and Follow-on Drugs

Firm Type	New Drugs	Follow-on Drugs
A. Brand Name	NDS	SNDS
	NDS FIC	SNDS FIC
	NDS NAS	SNDS NAS
B. Generic	-	ANDS
	-	SANDS

B. DRUG PATENTING

We also conducted a study on the relationship between drug approval, drug patenting, and drug litigation. This involved statistical analysis of patenting patterns associated with sixteen of the most profitable drug products in Canada.[101] We chose the top sixteen drugs for our initial study given that this cohort was likely to display the strongest patenting and patent listing patterns. This is because pharmaceutical companies have a vested interest in protecting the market on their most profitable drugs, and the primary means of doing so is via patenting. Each of the drugs studied under the patent analysis was approved in Canada between 2001 and 2008 and were analyzed as part of the drug approval data shown in Figures 1–3. Unlike the drug approval study, the drug patenting study was not restricted to a certain time period. This was necessary because many of the patents on drug products for which approval was granted during the 2001–2008 test period were filed and issued before 2001.

A detailed patent search of the Canadian Intellectual Property Office (CIPO) database was conducted for each drug approved and analyzed in Sa-

101. Andrew Humphreys, *MedAdNews 200—World's Best-Selling Medicines*, MEDADNEWS, July 2007. The drugs analyzed were: Lipitor,™ Advair,™ Plavix,™ Nexium,™ Norvasc,™ Zyprexa,™ Diovan,™ Risperdal,™ Effexor,™ Pantoloc,™ Singulair,™ Seroquel,™ Prevacid,™ Crestor,™ Prilosec,™ and Altace.™ Note that the list does not correspond literally to that in the United States. Rather, we chose for initial study, working backwards from number one, a group of 16 drugs that were on the U.S. list and which also had approval dates between 2001 and 2008 as identified in Sawicka & Bouchard, *supra* note 35.

wicka & Bouchard.[102] The CIPO search employed broad search terms for each drug in question with an effort to cast the widest possible net so that even patents with a remote possibility of being relevant would be returned by the search engine and made available for analysis and classification. The search was designed to return all patents owned by or assigned to the drug's manufacturer—including those owned by its parent company, subsidiaries, and partners—that made claims regarding the specific medicinal ingredients associated with the drug or claims regarding the general therapeutic class(es) to which the drug belongs. The patent search for each drug comprised two search strings: (a) a specific search string that returned patents likely to be relevant to the specific drug in question; and (b) a general search string that returned patents likely to be relevant to the general therapeutic class associated with the drug in question. Both are provided in Table 2.

Table 2: Search Strings for Data Collection and Analysis.

Search String	Boolean Operators
A. Specific Search String	((chemical name)<OR>(code name)<OR>(brand name)<OR>(chemical class)<OR> (chemical formula))<AND>(owners<IN> OWNER)<AND>(PAPD>=1867-07-01)<AND> (PAPD<=study start date)
B. General Search String	((*therapeutic class*)<OR>(*active site*))<AND><NOT>(*chemical name*)<AND><NOT> (*code name*)<AND><NOT> (*brand name*)<AND><NOT>(*chemical class*)<AND><NOT> (*chemical formula*)<AND>(*owners*<IN> OWNER)<AND>(PAPD>=1867-07-01)<AND> (PAPD<=*study start date*)

The specific search string used Boolean operators to return all patents owned by the drug manufacturer or its affiliates that mention either the drug's chemical name(s), code name(s), brand name(s), chemical class(es), or chemical formula(e), and have priority dates between the date of Canada's Confederation and the start date of the study. Databases such as CIPO and the Canadian Patent Register (CPR), their American counterparts, the U.S. Patent and Trademark Office (USPTO) and Orange Book (OB) databases, as well as secondary sources, were used to acquire an exhaustive list of all possible chemical names, codes names, brand names, and chemical classes associated with a particular drug. In determining the chemical formula, precedence was given to formulae expressed in patents found on CIPO and USPTO databases. The owners referred to within the search string refer not only to a drug's manufacturer but also to its possible parent company, sub-

102. *See* Sawicka & Bouchard, *supra* note 35.

sidiary and partner(s). This list of owners was cross-referenced using CIPO, CPR, USPTO, and OB databases as well as searches of case law and secondary sources where necessary.

The general search string used Boolean operators to return all patents owned by the drug manufacturer or its affiliates, not previously found by the specific search string, that mention the therapeutic class(es) to which the drug belongs or make specific reference to the drug's active site. The therapeutic class and active site of a drug are obtained by reference to CIPO, CPR, USPTO, and OB databases, and secondary sources such as company websites and Internet searches. These sources were used to acquire an exhaustive list of all possible chemical names, codes names, brand names, and chemical classes associated with a particular drug.

Combined, the two search strings return a broad list of potential patents owned or assigned to the Canadian manufacturer or its subsidiaries or partners. The legitimacy of the search terms was confirmed using Health Canada's drug approval data, as well as manufacturer, securities, and exchange websites, from which ownership histories were ascertained. Patents were individually inspected and pruned when deemed irrelevant to drugs in the study. The USPTO database, which provides a history of prior art, was also used as a means of cross-referencing patents for relevance. Relevant patents were sorted by priority date and cross-referenced with the patents registered on the CPR pursuant to linkage regulations.

C. PATENT LISTING AND LITIGATION

We quantified patents identified using the search method that were also listed on the Canadian Patent Register (CPR) under the NOC Regulations. Patents listed on the register can be litigated numerous times since they can be listed for multiple Drug Identification Numbers (DINs) under the NOC Regulations. Patent listing is a critical step to potential extension of patent monopolies for drugs coming off patent protection because generic firms must demonstrate in litigation that each patent on the list is either invalid or not infringed by the generic product to obtain market approval. For our purposes, only the date of first instance (the earliest date on which the patent was registered) for each patent was collected and analyzed.

In addition to analyzing patents listed on the patent register, we also investigated the case law pertaining to patents litigated under the NOC Regulations. We assessed the number and types of trials, the number of patents litigated in these trials, the number and types of legal decisions on listed and litigated patents (motions, trial and appellate decisions), whether listed patents were valid and infringed (brand name victory) or invalid and not in-

fringed (generic victory), and the theoretical and actual extension of patent monopolies via the operation of linkage regulations.

D. ANALYTICAL MODEL

The third element of the study was the synthesis of empirical data from approval, patenting, and litigation studies into an analytical model. The focus of the analysis is on the impact of regulatory incentives designed to facilitate breakthrough pharmaceutical innovation by providing strong IPR rights to firms. Throughout Part III, we compare data relating to the time courses of varying types of drug approvals with concomitant drug patenting, patent listing, and litigation data. Particular attention was given to the synchronization, if any, of approval, patenting, listing, and litigation data to the times for establishment of the NOC Regulations and proposal of the Progressive Lifecycle Framework, as both were intended to facilitate enhanced access to novel therapeutic products in exchange for strong IPR rights. However, since most of the data relate to the period before the Progressive Lifecycle Framework was fully integrated into Canadian law, the majority of the analysis relates to the linkage regulations. The analysis has been cast in terms of a complex adaptive innovation ecology in Section IV.D of the Article.

E. DATA ANALYSIS

Drug approval, patenting, patent listing, and litigation data were collected, statistically analyzed, and graphed as described previously[103] using a combination of Excel® (Microsoft. Corp., Redmond, WA), GraphPad Prism® (Graphpad Software Inc. La Jolla, CA), and SigmaPlot® (Systat Software, Inc. San Jose, CA). Legal decisions relating to listed and litigated patents were obtained using Quicklaw™ (Lexis Nexis®) and Westlaw® (Thomson Reuters®). Economic data relating to prescribed pharmaceuticals were obtained with permission from IMS Health Inc. (Canada) and from published reports from the Canadian Institute for Health Information (CIHI). Patent data were obtained from Canadian (CIPO) and U.S. (USPTO) patent databases.

III. RESULTS

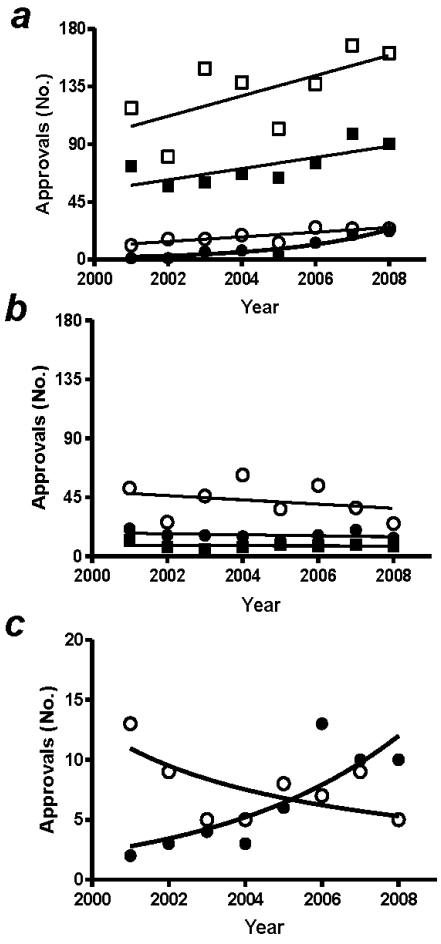
A. DRUG APPROVAL

To empirically investigate the relationship between drug regulation and innovative therapeutic product development, we first reviewed market authorizations for pharmaceuticals in Canada over the period from 2001–2008

103. *See id.*

(test period).[104] 2001 was taken as the starting point for analysis, as major amendments to the nation's food and drug legislation and regulations were made at that time which affected both the goals and mechanism of national drug regulation.[105] Market authorizations in Canada are referred to as Notices of Compliance (NOCs). We analyzed a total of 3,837 NOCs. Of these 45% were administrative in nature, e.g., product manufacturer or name change. This left 2,122 approvals for detailed analysis. These approvals were attached to 608 marketed drug products, amounting to an average of 3.5 approvals per product.

Figure 1: Shifting Patterns of Drug Approval and Drug Regulation During the Period 2001–2008



104. *See also* Bouchard & Sawicka, *supra* note 29; Sawicka & Bouchard, *supra* note 35.
105. Sawicka & Bouchard, *supra* note 35, at 107.

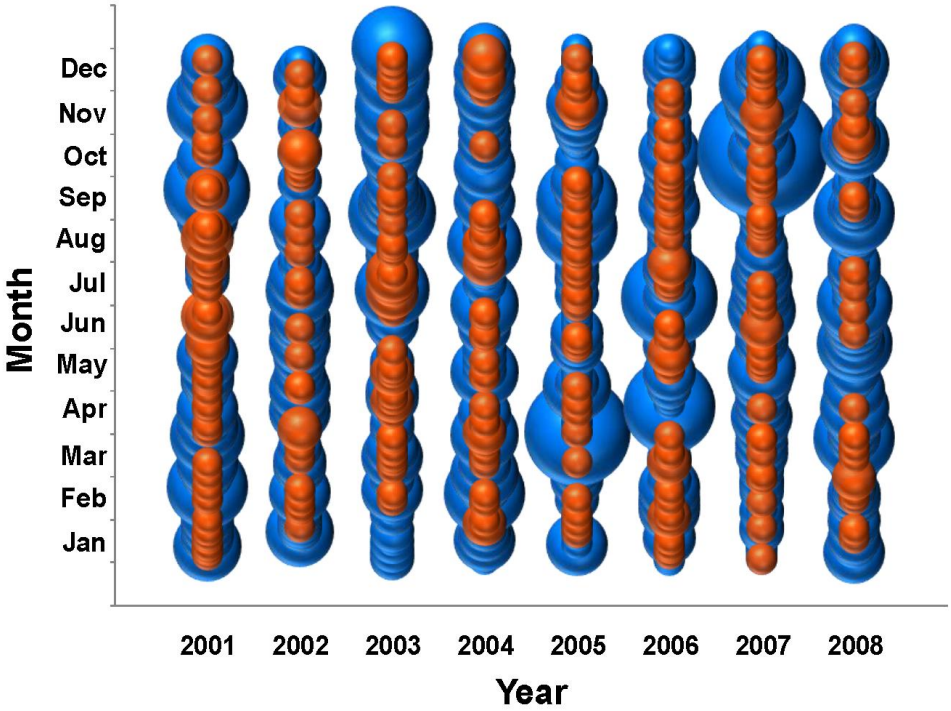
a. Market authorizations for several types of "follow-on" drug increased over the 2001–2008 test period. This includes brand name Supplemental New Drug Submission (SNDS: □) and SNDS First In Class (SNDS FIC: ●) approvals, and generic Abbreviated New Drug Submission (ANDS: ■) and follow-on Abbreviated New Drug Submission (SANDS: ○) approvals. ***b.*** In contrast, approvals granted to brand name firms for "new" drug submissions declined from a smaller baseline over the same period. This included approvals from New Drug Submission (NDS: ○), New Active Substance (NAS: ●) and NDS First In Class (NDS FIC: ■) streams. ***c.*** Expedited review pathway for drug approval is shifting towards probationary-type approval consistent with emerging lifecycle models of regulation: Expedited drug approvals with no post-market evidentiary obligations (Priority Review: ○) decreased over the 2001–2008 test period while those with significant post-market obligations conditions (NOC/c: ●) increased steeply over the same time frame.

Using the classification scheme described in Part II and summarized in Table 1, we found that follow-on drugs constituted the vast majority of drugs approved in the domestic market over the period 2001–2008. For example, in 2001 the total number of follow-on approvals was 2.39 times greater than that for total new drug approvals. This constituted 70.5% of all approvals in Canada over the test period and 65.33% of approvals granted to brand name pharmaceutical firms. As shown in Figure 1a, this trend intensified over the test period. By 2008, the number of follow-on approvals was 6.32 times greater than new drug approvals. This constituted 86.4% of all approvals in Canada and 86.02% of brand name approvals over the same time frame. Approvals directed to line extension drugs (SNDS: □) accounted for 34% in 2001, increasing to 47% in 2008. By comparison, the more innovative supplementary first in class drugs (SNDS FIC: ●) made up the smallest fraction of all follow-on approvals (5.4% in 2001). While the number of SNDS FIC approvals was small, it nevertheless increased sharply over time, from 1 in 2001 to 22 in 2008. As shown in Figure 1a, follow-on approvals granted to generic firms based on bioequivalence to previously marketed products also increased significantly over the test period. Both standard (ANDS: ■) and supplementary (SANDS: ○) generic approvals increased by 28.6% and 118.2%, respectively, over 2001 values. Therefore, all four categories of follow-on drugs increased over the test period.

Figure 1b demonstrates opposite trends for all new drug categories over the course of the test period, and that these changes took place from a smaller baseline. Approvals granted for all new drugs combined declined from 29.5% of total approvals in 2001 to 13.69% in 2008. Similarly, approvals granted to brand name pharmaceutical firms decreased from 34.67% of total approvals in 2001 to 13.44% 2008. These data represent a reduction of 55% and 48% in total approvals and approvals granted to brand name firms respectively over the eight year test period. As the regression lines illustrate, the approvals for all three new drug metrics (NDS: ○; NAS: ●; NDS FIC: ■)

declined steadily over the course of the test period.

Figure 2: Time Series Distribution for New and Follow-on Drug Approvals During the Period 2001–2008



Bubbles represent approvals granted per day for "new" (●) and "follow-on" (●) drugs as defined in the text accompanying Fig. 1. Bubble diameter is a linear representation of the number of approvals granted per day distributed over the course of the test period expressed yearly and monthly. The data illustrate that both new and follow-on drug approvals were well spaced out over the course of the test period rather than being aggregated in a given month or year, particularly when viewed over the course of the entire eight year test period.

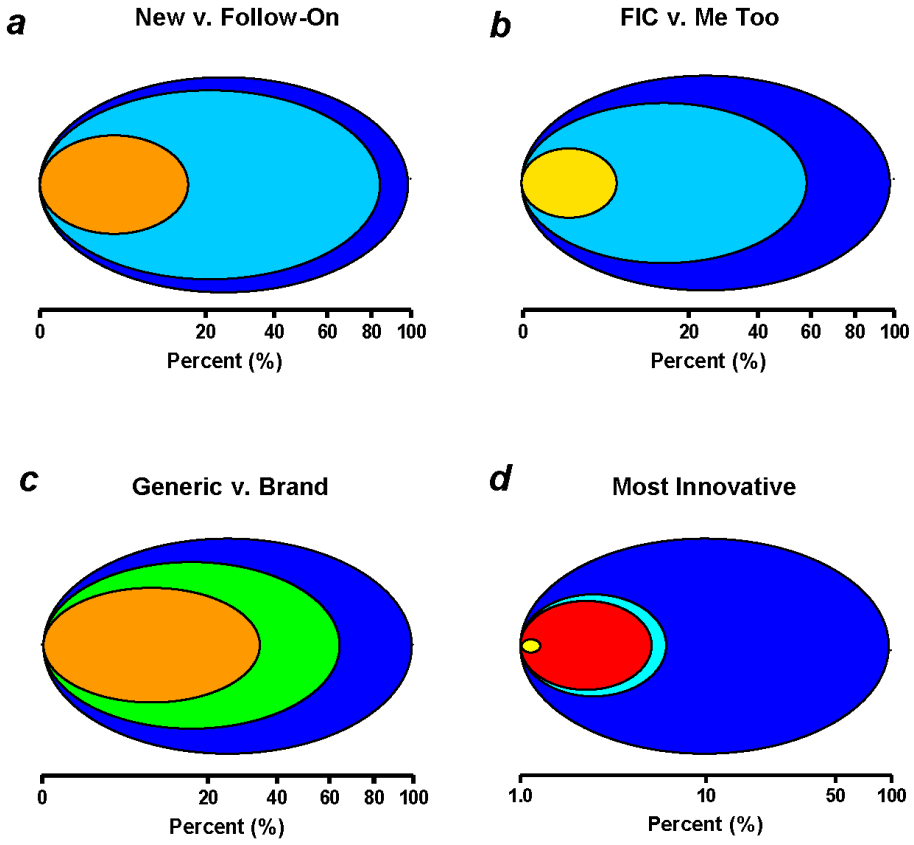
Time series plots for new and follow-on approvals are presented in Figure 2. Approval data for both classes of drugs are expressed as approvals per day plotted by month and year over the test period. The data illustrate that both new (●) and follow-on (●) drug approvals were well spaced out over the course of a given year rather than aggregated in a given month or year, particularly when viewed over the course of the entire test period. Therefore, there was no daily or monthly variation skewing yearly averages as discussed in relation to Figures 1 and 3. Comparative data for all new and follow-on approval categories in 2001 and 2008 are provided in Table 3.

Table 3: Comparison of 2001 and 2008 Drug Approval Data

Drug Type	2001		2008		Δ (%)
	N=	% Total	N=	% Total	
A. New Drugs	52	20.4%	25	83.3%	-51.9%
NDS	52	100.0%	25	100%	-51.9%
NDS FIC	12	23.1%	8	32.0%	-33.3%
NDS NAS	21	40.4%	14	56.0%	-33.3%
B. Follow-On Drugs	203	79.6%	275	91.7%	35.5%
SNDS	118	58.1%	161	58.5%	36.4%
SNDS FIC	1	0.5%	22	8.0%	2100.0%
ANDS	73	36.0%	90	32.7%	23.3%
SANDS	11	5.4%	24	8.7%	118.2%

Figures 3a–d are area diagrams illustrating *cumulative* approval data for various categories of new and follow-on drug products. As shown in Figure 3a, only 16% (n=338) of the 2,122 drugs approved over the period 2001–2008 were deemed to be "new" drugs. This refers to NDS submissions, including those directed to FIC therapies and those including an NAS. By contrast, 84% (n=1,784) of approved drugs were "follow-on" in nature, including brand name SNDS approvals, generic ANDS and SANDS approvals, and brand name SNDS approvals directed to FIC therapies.

Figure 3: Profile of Pharmaceutical Innovation in Canada between 2001–2008



a. New v. follow-on approvals. Of total drugs approved over the test period, 15% constituted New Drug Submissions (NDS: ●) while 84% were for "follow-on" drugs (SNDS, ANDS and SANDS: ●). ***b.*** Types of follow-on approvals. Of follow-on approvals, 6.1% were for supplementary "First in Class" (SNDS FIC: ●) drugs while 59% were for "Me-Too" drugs (●). ***c.*** Brand name v. generic approvals. Of all drugs approved during the test period, 65.5% of approvals were granted to brand name drug companies (NDS and SNDS: ●) and 34.5% to generic companies (ANDS and SANDS: ●). ***d.*** Most innovative drugs. While 6.5% of approvals during the test period were directed to New Active Substances (NAS: ●) and 5.3% of all NDS and SNDS submissions were approved under an expedited review process (Priority Review and NOC/c: ●), only 1.23% of all drugs approved over the period 2001–2008 were also directed to FIC therapies and contained an NAS (●). Areas are approximations of calculated means for the entire test period. Note that area scales are linear for panels ***a–c*** and log for panel ***d***.

Figure 3b shows the results of a more nuanced analysis of follow-on drugs, this time focusing on comparison of Me Too and FIC drugs. Of all drugs approved between 2001 and 2008, 59% (n=1,252) were Me Too. Of note, the fraction of Me Too drugs was substantially greater than all FIC

drugs, irrespective of whether they were NDS or SNDS (6.5%; n=138). The requirements for NDS and SNDS FIC and Me Too drugs are summarized for convenience in Table 4.

Table 4: Classification Scheme for First in Class and Me Too Drugs

Route	FIC	Me Too
A. NDS	New Chemical Form -or- New Use/Indication	Change in Benefit:Risk
B. SNDS	New Chemical Form -and- New Use/Indication	Change in Chemical Form -and- Change in Benefit:Risk

Generic drugs were the final follow-on category to be assessed. The split between total brand name and generic drugs approved from 2001 to 2008 is shown in Figure 3c. Of all drugs approved over the test period, 65.5% were directed to brand name products while the remaining 34.5% were directed to generic products.

Data for the most innovative drugs approved during the test period are given in Figure 3d. Only a small fraction (6.1%) of drugs approved (n=130) during the test period contained an NAS. Similarly, of 2,122 drugs approved, only 5.3% (n=112) went through the two expedited approval streams (Priority Review or NOC/c), and of these only a small number (n=26) were also directed to FIC therapies and contained an NAS. This amounted to 1.23% of total drug approvals over the eight-year test period and 1.87% of total brand name approvals over the same period. These results illustrate that the typical drug approved by Canadian regulators over the period 2001–2008 was most likely to be a drug approved via the SNDS stream rather than a new drug approved via either the NDS stream or either expedited stream (Priority Review or NOC/c). The likelihood that a drug approved during the test period satisfied the most stringent requirements for a breakthrough drug was close to zero (1.23%).

As discussed supra, there are two forms of expedited drug approval in Canada: "Priority Review" and approval via the "NOC with conditions" (NOC/c) pathway.[106] Priority Review allows appropriate candidates to be shifted forward in the approval queue without a change in evidentiary requirements for safety and efficacy required for conventional NDS approval. Drug candidates must be directed to treatment of a serious, life-threatening,

106. *Id.* at 87.

or severely debilitating disease with an unmet medical need or for which a substantial improvement in the benefit-risk profile is demonstrated.[107] By contrast, the NOC/c pathway allows a drug to gain market access prior to completion of traditional Phase 3 clinical trials, provided that it is directed to a serious, life-threatening, or severely debilitating disease for which no drug is marketed or where the candidate presents a better overall benefit-risk profile than existing therapies. Unlike the Priority Review stream, continuing approval via the NOC/c stream is contingent upon whether pharmaceutical sponsors meet the conditions assigned to the NOC/c. For this reason, NOC/c approval is a reasonable proxy for emerging lifecycle models of drug regulation.[108]

Data in Figure 1c suggest that Canadian regulators may be shifting away from Priority Review as the dominant mechanism for expedited review towards the NOC/c pathway. Priority Review approvals (○) decreased from 14 in 2001 to a low of 6 in 2008, declining 57% over the eight year test period. By comparison, the number of NOC/c approvals (●) escalated sharply over time, from a minimum of 2 in 2001 to a maximum of 13 in 2006 (stabilizing at 10 in 2007–2008). Compared to the 57% decline in the number of Priority Review approvals, peak NOC/c approvals increased by 650%. The totals for both streams over the test period were not dissimilar; 61 and 51 for Priority Review and NOC/c, respectively. However, as illustrated by the data and fits in Figure 1c, the trends for the two pathways crossed in 2005.

Of interest, the legal basis for Priority Review and NOC/c approval are not expressly provided for under the current Food and Drugs Act[109] or regulations.[110] Rather, both are grounded in administrative instruments known as "guidance documents" that do not have the force of law.[111] Data described in Figure 1c therefore demonstrates that Canadian regulators are already "anticipating" the lifecycle regulatory framework proposed in Bill C-51,[112] along with its recalibrated balance of pre-market and post-market access, safety, and efficacy. Together, the data in Figures 1–3 suggest that Canadian regulators are focusing on faster approval with enhanced post-market surveillance, whiles approval is geared more towards follow-on rather than towards breakthrough drug development.

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107. HEALTH CANADA, GUIDANCE FOR INDUSTRY, *supra* note 30, at 1–2.

108. For a discussion of this issue see Section I.B.1 of this Article and Bouchard & Sawicka, *supra* note 29, at 105–06.

109. *See* Food and Drugs Act, R.S.C., ch. F-27 (1985).

110. *See* Food and Drug Regulations, C.R.C., ch. 870 (2009).

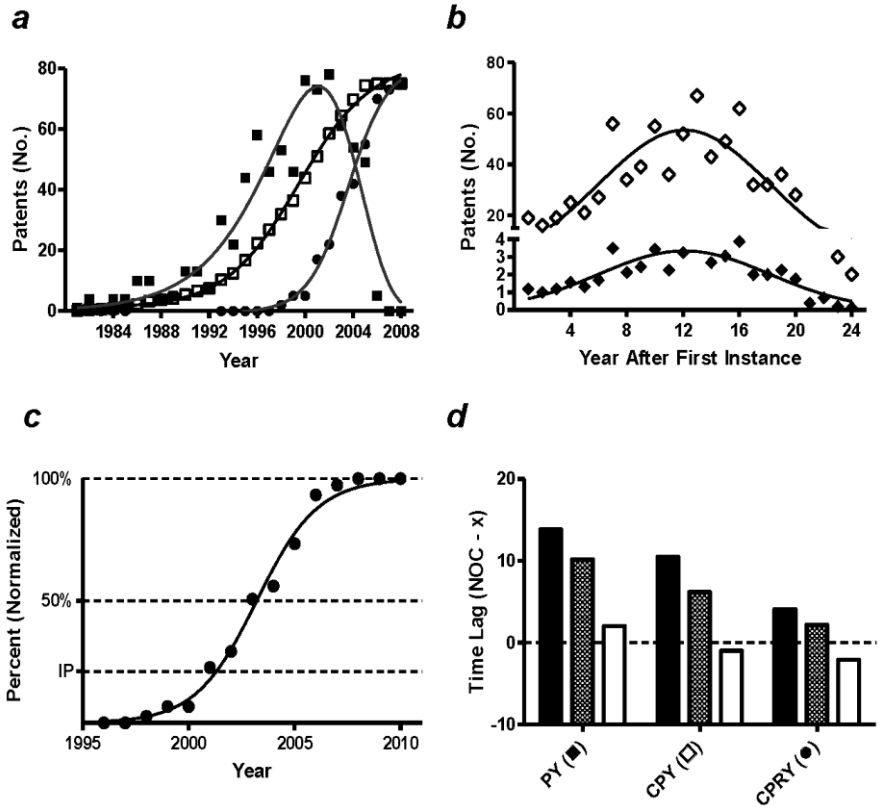
111. *See* Bouchard & Sawicka, *supra* note 29, at 52.

112. Sawicka & Bouchard, *supra* note 35, at 117.

B. DRUG PATENTING

Figure 4 shows data relating to drug patenting and patent listing of drugs approved for sale in Canada during the period 2001–2008. The data are for 16 of the most profitable drugs sold in Canada for which an NOC was granted during the test period (approval subset). The list parallels the top 16 drugs sold in the United States during the same period.[113]

Figure 4: Patenting and Patent Listing Patterns Associated with Drug Approval



a. Total patents issued by year associated with a sub-set of sixteen top selling drugs (■); cumulative number of patents associated with the sub-set (□); and cumulative number of patents listed on the patent register under linkage regulations associated with the sub-set (●). Note the strong convergence of total and listed patents over the course of the test period. ***b.*** Total (◇) and average (◆) number of patents on approved drugs within the subset plotted as a function of the time after the priority date on which the first patent on the subset was issued. ***c.*** Method used to calculate the temporal gap between the date of mean drug approval on the patent subset (2005) and the inflection point (IP), 50th, and 100th percentile of normalized maximum drug patenting and approvals. Data are from the cumulative number of patents (●) above. ***d.*** Graph expressing the temporal relationship between drug approval

113. Humphreys, *supra* note 101. For more information, see Part I.

and the IP, 50th, and 100th percentile of maximal normalized patents granted per year (PY), cumulative patents per year (CPY), and cumulative patents listed on the patent register per year (CPRY). Time points are calculated as the difference between the date of drug approval (NOC) and the date of the IP, 50th, and 100th percentile (NOC-x). The data suggest that drug patent listing may be a better proxy for drug approval than drug patenting.

As illustrated in Figure 4a, total patents granted on the approval subset had a bell-shaped distribution (Gaussian; R^2=0.91), peaking in 2001 (■). There were 772 patents on 16 products, corresponding to an average patent per product ratio of 48:1. The calculated inflection point, representative of the take-off point from baseline, for total patents issued yearly occurred about 1991 (1991.35). This was just before the linkage regulations came into force in 1993. That the inflection point preceded the NOC Regulations is not surprising in light of the significant negotiations leading up to TRIPS and the coming into force of the linkage regulations regime. Cumulative patents for the subset rose over time in a manner that was well described by a sigmoidal function (□; R^2=0.99), peaking at about 2004. The calculated inflection point (1994.70) was slightly later than that calculated for total patents, occurring just after the linkage regulations came into force. Figure 4b (top) gives the same data re-plotted as a function of the year after the first patent was issued. Patents on approved drugs were granted over a relatively long term of 25 years (◇), peaking at 77 patents per year on the 12th year after the first patent was granted. As illustrated in Figure 4b (◆), this amounted to an average of 3.34 patents per product per year.

C. PATENT LISTING AND LITIGATION

Over the last decade, there have been increasing claims to the effect that the linkage regulation regime is used as more of a sword than a shield by brand name pharmaceutical firms.[114] Figure 4a illustrates the manner in which

114. *See generally* ROY J. ROMANOW, COMM'N ON THE FUTURE OF HEATH CARE IN CAN., BUILDING ON VALUES: THE FUTURE OF HEALTH CARE IN CANADA: FINAL REPORT 208–210 (2002), *available at* http://dsp-psd.pwgsc.gc.ca/Collection/CP32-85-2002E.pdf (discussing the negative impact of evergreening by pharmaceutical corporations to extend the life of their patents and the costs associated with preemptory litigation on patent protection disputes); Bouchard, *PHOSITA*, *supra* note 73, at 46–52 (arguing that the procedures associated with linkage regime have led to unoriginal line extension patents resulting in reduced competition between firms and restricted consumer access to essential medications); Bouchard, *Scientific Research*, *supra* note 73 (arguing that that obviousness analysis by courts in NOC litigation allows pharmaceutical corporations to maintain a monopoly over their patented chemical compounds by setting a low bar for what is "nonobvious"); Caffrey & Rotter, *supra* note 84 (discussing the use of the Hatch-Waxman Act procedures by pharmaceutical corporations to maintain elevated prices, and the needs for reform that favors consumer interests); Hore, *supra* note 73, at 8–10 (discussing that NOC regulations lead to extended litigation between pharmaceutical corporations and potential generic produces that often leave infringe-

patents for the approval subset were listed on the patent register over the test period. The time course for cumulative listed patents (●) was well described by a sigmoid function (R^2=0.99), with a relatively steep slope, an inflection point near 2001 (2001.10), and an apparent peak in 2008. Importantly, the curves for cumulative patents (□) and the fraction of patents that were listed on the patent register (●) converged strongly over time. This result supports the conclusion that brand name firms are listing patents they obtain on the patent register in a timely fashion in order to delay generic entry.[115]

Of 772 patents granted on the approval subset, 77 were listed on the patent register between 1998 and 2008. On average there were 4.81 listed patents per product. As indicated by the difference between the average number of patents per year (3.34) and the average number of listed patents per product (4.81), domestic linkage regulations allow patents to be listed on more than one product. Unlike drug patenting, which occurs only in an anterograde direction (i.e., patents must be new, non-obvious, and have utility over the prior art), patents may be listed on the patent register in either an anterograde or retrograde direction. For example, originating patents relating to proton pump blockers may be listed not just for first generation product Losec® (racemic mixture of R and S omeprazole Mg^{2+}) but also the second generation product Nexium® (S enantiomer, esomeprazole Mg^{2+}), and vice versa.

We next investigated the temporal relationship between NOC grant, patent issue and patent listing. From each of the curves in Figure 4a, we calculated three values: (a) the inflection point at which the data deviated most strongly from baseline values (closed bars), and the point at which each curve reached the (b) 50th (hatched bars) and (c) 100th percentile (open bars) of normalized maximum values. The inflection point was calculated as the zero point of the second derivative of the data trendlines. Each of the three values was then plotted as a function of the average date on which the subset received marketing approval (2005). This was done to obtain a measure of the delay between drug approval and drug patenting and listing. The procedure is demonstrated for cumulative patent listing data in Figure 4c (●).

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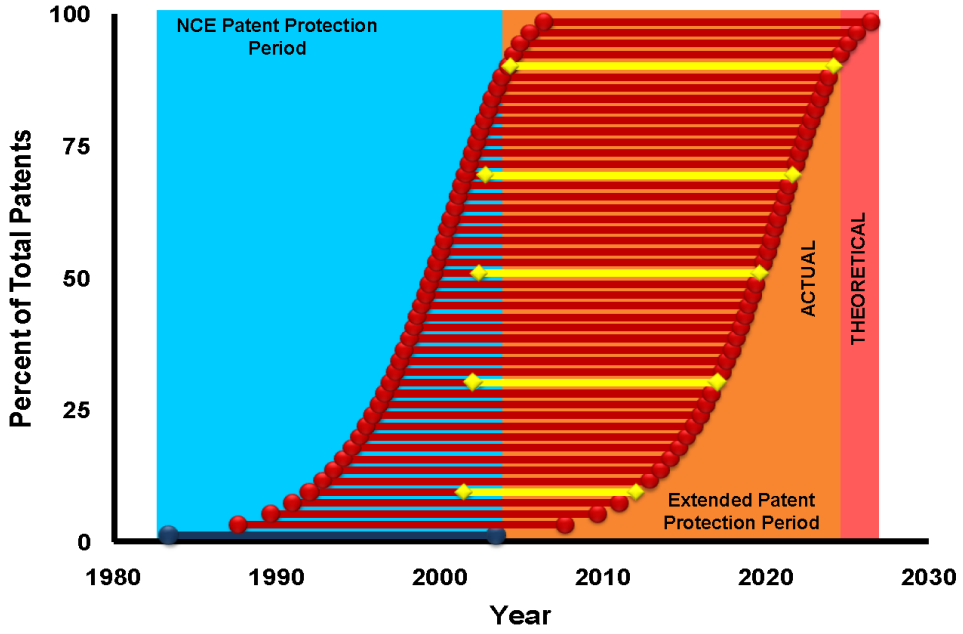
ment claims unresolved); Jaffe, *supra* note 94.

115. AstraZeneca Can. Inc. v. Canada, [2006] 2 S.C.R. 560, ¶ 29 (Can.) (discussing the ambiguity of NOC Regulations and that requirements for filing prohibition motions could be interpreted so as to force generic producers "to address new patents as fast as [pharmaceutical corporations] could have them added to the . . . list"); *see generally* Bouchard, *PHOSITA*, *supra* note 73, at 50 (discussing how the low standard for "incremental line extension" patents allows the corporations to register patents for uninventive products after minimal investment, keeping generic products off the market for longer).

As illustrated by the bar graphs in Figure 4d, there was a significant lag between the date on which NOCs were granted and the dates on which patents on the same drug product were granted. This pattern was observed independent of whether patents were expressed by year of grant (Patent per Year, or PY) or cumulatively (Cumulative Patents per Year, or CPY). This is not surprising in light of the regulatory lag between drug patenting and drug approval. The data were different however for patent listing (Cumulative Patents Registered per Year, or CPRY). As shown in Figure 4d, average data for both the inflection point and 50th percentile exceeded the null point by only 4 and 2 years, respectively. This can be compared with 10 and 8 years for corresponding data for cumulative patents (CPY). The lag between drug approval and patent listing was even greater for patenting data expressed as a function of year of grant (PY). Of interest, the calculated values for the 50th percentile and peak patent listing for CPRY were 1–2 years on either side of the null point. This result indicates there was virtually no significant lag between drug approval and patent listing as the test period progressed. While the data obtained do not provide conclusive evidence for a causal relationship between drug regulation and drug development, they demonstrate that patent listing is a substantially better proxy for drug approval than drug patenting.

Figure 5: Extension of Patent Monopoly for Marketed Drugs via Operation of Linkage Regulations



Period of extended patent protection for averaged drugs in the subset (n=16). Left and right sigmoid curves represent cumulative patent protection start and end dates. The term of pa-

tent protection was deemed to begin on the priority date. Terms are shown for the "originating patent" on the New Active Substance/New Chemical Entity (●; n=1) and all "subsequent patents" (●; n=21). The date on which patents were listed on the register is also shown (◆; n=5). The duration of theoretical and actual patent protection under linkage regulations associated with originating and subsequent patents are illustrated by representative horizontal lines and shading along the time axis. Note the period of patent protection associated with originating patents lasted about 20 years (■), from 1983–2003. In comparison, the duration of extended patent protection associated with all "subsequent patents" was much longer (■), lasting from about 1987 to 2028. Of the 48 patents granted per drug, an average of 5 were listed on the patent register. The term of protection associated with these patents ran from 1993–2025 (■). This yielded an actual extended period of patent protection of 22 years beyond that afforded by the originating patent. Note that due to strategic listing of patents on the patent register (◆), there was little difference between theoretical and actual patent protection under linkage regulations.

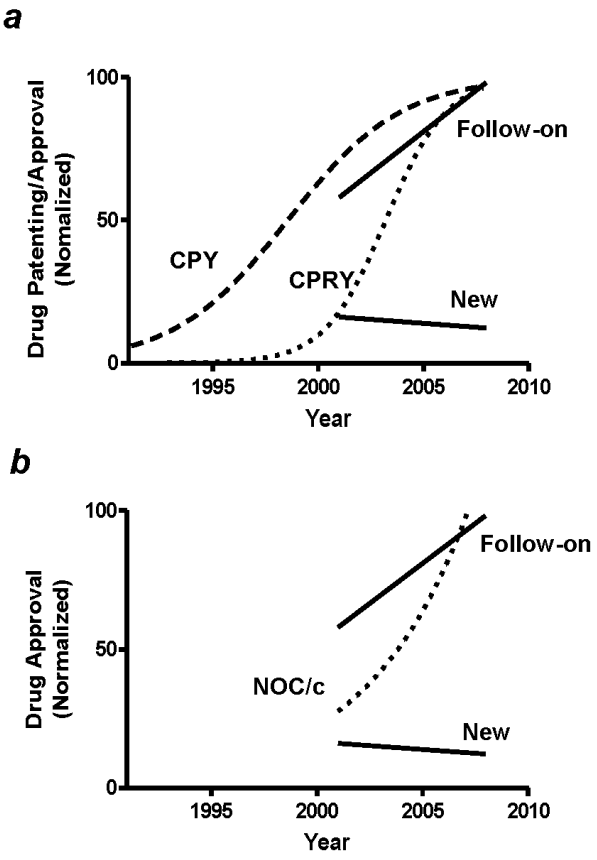
Given the results in Figure 4, we further probed the nexus between drug approval, drug patenting, and patent listing, particularly as it relates to potential extension of the term of patent protection afforded to drugs that are already approved in Canada. Figure 5 shows a comparison of potential and actual periods of extended patent protection for the average drug product in the approval subset due to operation of linkage regulations. Here "potential" is used to refer to the hypothetical extension of patent protection under patent legislation and linkage regulations if all patents granted were in fact listed on the patent register. In comparison, the "actual" term of extended patent protection refers to the extension of the duration of patent protection beyond that afforded by the originating patent alone as a result of those patents actually registered on the patent list. The sigmoid curves represent the start and end dates for the potential term of patent protection as a function of patents associated with approved drugs. The term starts with the priority date of the "originating patent," e.g., the first patent on the drug, typically that on the NAS/NCE (●), and ends 20 years from the filing date of the originating patent plus the cumulative terms of all "subsequent patents" (●) associated with the marketed drug. This is illustrated by the corresponding horizontal lines and shading in Figure 5. Patents actually listed on the register are represented by appropriate symbols (◆) and horizontal patent term lines.

The average period of patent protection associated with originating patents was about 20 years, from 1983–2003. This represents an average of patent terms before (17 years from date of grant) and after (20 years from filing date) amendments made to the Patent Act pursuant to TRIPS. In comparison, the duration of potential extended patent protection associated with subsequent patents was about 2-fold longer, lasting from about 1987 to 2026. This yields a term of extended patent protection due to operation of linkage regulations of about 43 years per drug on average. However, this calculation

does not reflect the actual period of extended patent protection, which would only be a function of cumulative terms for patents actually listed under the NOC Regulations on the register. Of the average of 48 patents per product on the approval subset, 10% (4.81 patents per product) were actually listed on the register.

Termination of listed patents was spaced fairly evenly between 2010 and 2025 rather than being clumped together at the front end of the data set. The even distribution of listing resulted in the extension of the term of patent protection from the end of the NAS patent in 2003 to termination of the latest listed patent in 2025. The extension of the average patent term owing to linkage regulations amounts to an increase of 22 years, representing a doubling of the duration of patent protection beyond that associated with the originating patent. As illustrated by the appropriate symbols (◆) and shading in the figure, there was little difference between potential and actual terms of patent extension for the approval subset under the NOC Regulations. This was due to strategic timing of patent listing by brand name drug firms e.g., firms stagger the registration of their strongest patents to obtain the longest period of protection. Of note, comparison of data in Figures 3 and 5 demonstrate that while the average drug approved in Canada over the test period has an arguably low innovative value, the average period of patent protection afforded to products in the approval subset is in fact quite substantial.

Figure 6: Comparison of the Timing of Trends for Drug Innovation, Lifecycle Regulation, Patent Grant and Patent Listing



a. Overlay of time courses of fits to normalized cumulative patents per year (CPY; long dash), cumulative listed patents per year (CPRY; short dash), new drug approvals (New; downward linear) and follow-on drug approvals (Follow-on; upward linear). Data for "new" and "follow-on" innovations were calculated from NDS and SNDS/ANDS/SANDS curves in Figs. 1a and 1b. Drug patenting and listing data are from Fig. 4a. ***b.*** Overlay of new drug approvals and follow-on drug approvals from panel *a* and life-cycle-based NOC/c approvals (NOC/c; short dash). Data for expedited review were taken from Fig. 1c. Comparison of these curves suggests that steep time-dependent changes in patent grant, patent listing or NOC/c approval as proxy for lifecycle regulation appear to be poorly correlated with, and thus to provide poor incentives for, breakthrough drug development as measured by new drug approval data.

The importance of the timing of shifts in innovation profiles, expedited drug approval, drug patenting, and patent listing is underscored by the data in Figure 6. In this analysis, drug patenting and listing represent patent incentives for innovation, whereas expedited drug approval is taken as a measure of lifecycle-based regulatory incentives for innovation. The data for "new"

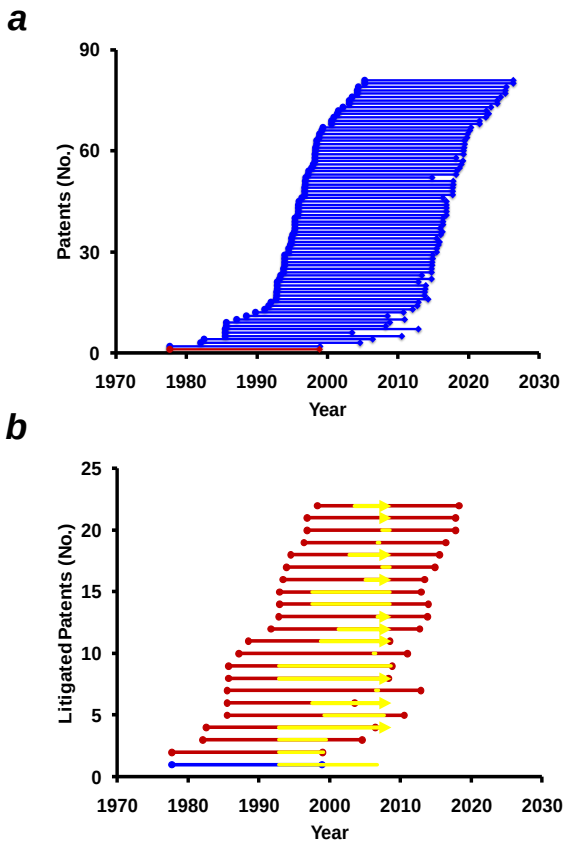
and "follow-on" innovations represent the fits to NDS data and SNDS, ANDS, and SANDS data from Figures 1a and 1b. Data for lifecycle regulation were taken as the fit to NOC/c data from Figure 1c. Drug patenting and patent listing curves are those from Figure 4a.

A comparison of fitted curves in Figure 6 indicates that neither the steep time-dependent changes in patent grant and patent listing preceding (Figure 6a) nor the NOC/c approval in the midst of relatively linear trends for new and follow-on drugs (Figure 6b) appear to provide a measurable incentive for pioneering drug development, at least as reflected by the data and fits to new and follow-on drugs. That these trends (1) occurred before and during the comparatively linear changes in new and follow-on drug approval by regulators (Figures 1 and 6) and (2) were observed independent of the temporal association of drug approval, drug patenting, and patent listing (Figure 4d) suggests that the current basket of IPR rights targets provides a much stronger incentive for follow-on rather than pioneering drug development. The results demonstrate that pharmaceutical firms, when they so desire, are capable of responding rapidly and strongly to regulatory incentives in the context of drug regulation, but that this responsiveness has not extended to increasing the production of new and innovative drugs.

Finally, there has been sharp criticism of the practice of "evergreening" drug products via linkage regulations in the United States and Canada.[116] Evergreening refers to extending the market monopoly on a drug facing originating patent expiration through listing of further relevant patents on the patent register for minor modifications to the marketed drug. An example of this phenomenon from our data set is presented in Figure 7.

116. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007); Bristol-Myers Squibb Co. v. Canada, [2005] 1 S.C.R. 533 (Can.); Apotex Inc. v. Merck Frosst Canada Inc., [1998] 2 S.C.R 193 (Can.), ¶ 33; *see also* Caffrey & Rotter, *supra* note 84.

Figure 7: Example of Extension of Patent Monopoly for Omeprazole



a. Relative to the forms of drugs marketed between 2001–2008, 82 patents were granted in relation to Losec® and Nexium.® As observed for averaged data on the subset of 16 drugs, the timing of the grant and the duration of cumulative patents followed a sigmoidal course, with patent protection beginning in 1978 and extending to about 2025. The first regulatory approval for omeprazole was in 1989. Data for the first New Chemical Entity (●) and all subsequent patents (●) are provided. ***b.*** Of the 82 patents granted on the two drugs, 22 were listed on the patent register and litigated under linkage regulations. Priority dates and patent terms are represented by appropriate symbols (●) and lines. Initiation, duration and termination of litigation on individual patents are represented by orange lines. Completely solid orange lines represent completed litigation. Right-facing arrows (➞) represent litigation which is still ongoing e.g., where it has not yet been determined that the listed patent was valid and infringed (brand name victory) or invalid and not infringed (generic victory). For details of individual trials, see text.

Omeprazole, marketed in Canada as Losec® (Prilosec® in the United States) and the second generation product Nexium® are widely considered to be two of the most profitable drugs developed over the last several decades.

Not surprisingly, they have also been the subject of prolonged and highly contentious litigation in both the United States and Canada. The chemistry and mechanism of action of both drugs is highly similar. Indeed, as illustrated in Table 5, their chemical names and formulae are almost identical. The difference between the compounds, as alleged in litigation in both jurisdictions,[117] is that the magnesium salt form of omeprazole (Losec®) undergoes a chemical shift following ingestion that converts a portion of the racemic mixture that is potentially inactive to the fully active chemical form (Nexium®).[118] This chiral shift has been claimed to double the effective drug concentration.[119]

Table 5: Comparison of Omeprazole (Losec®) and Esomeprazole (Nexium®)

Band-Name	Formula	Chemical Name
Losec®	$C_{17}H_{19}N_3O_3S$	6-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl)-1*H*-benzo[*d*]imidazole
Nexium®	$C_{17}H_{19}N_3O_3S$	(*S*)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl]-*H*-benzoimidazole

Setting aside the scientific veracity of this claim for the moment, the question arises of how pharmaceutical firms are able to strategically employ minor, but potentially significant changes to already patented and marketed compounds in order to maintain market share, through either "blocking pa-

117. No final trial or appeal decisions relating to omeprazole enantiomers have been released to date. For a notation of the seven ongoing applications under the NOC Regulation pertaining to esomeprazole (Nexium®); *see* AstraZeneca Can. Inc. v. Apotex Inc., [2008] F.C. 537 (Can.). There are a number of Canadian and U.S. appeal decisions regarding enantiomers under the NOC Regulations. *See, e.g.*, AstraZeneca AB v. Ranbaxy Pharms., Inc., 2008 U.S. Dist. LEXIS 102097 (D.N.J. Dec. 15, 2008); Dr. Reddy's Labs, Ltd., v. AstraZeneca AB, No. 08-2496, 2008 U.S. Dist. LEXIS 66176 (D.N.J. Aug. 28, 2008); Ivax Pharms., Inc. v. AstraZeneca AB, No. 08-2165, 2008 U.S. Dist. LEXIS 66177 (D.N.J. Aug. 28, 2008); AstraZeneca v. Ranbaxy Pharms., Inc., No. 05-5553, 2008 U.S. Dist. LEXIS 6337 (D.N.J. Jan. 25, 2008); Pfizer Canada Inc. v. Minister of Health and Ranbaxy Laboratories Ltd. [2008] F.C.A. 108; Janssen-Ortho Inc. v. Novopharm Ltd., [2007] F.C. 809 (Can.); Apotex Inc. v. Sanofi-Synthelabo Can. Inc., [2006] F.C.J. 1945 (Can.). For additional judicial consideration of the anti-competitive and/or fraudulent nature of such patenting and marketing strategies, see: Walgreen Co. v. AstraZeneca Pharm. L.P., 534 F. Supp. 2d 146 (D.D.C. 2008); Pa. Employees Benefit Trust Fund v. Zeneca Inc., 499 F.3d 239 (3d Cir. 2007).

118. T. Lind et al., *Esomeprazole Provides Improved Acid Control vs. Omeprazole in Patients With Symptoms of Gastro-oesophageal Reflux Disease*, 14 ALIMENTARY PHARMACOLOGY & THERAPEUTICS 861 (2000). For a review of chirality in sulphur compounds, see Ronald Bentley, *Role of Sulfur Chirality in the Chemical Processes of Biology*, 34 CHEM. SOC. REV. 609 (2005).

119. Bentley, *supra* note 118.

tents" (inactive patents that nevertheless serve as a barrier to market entry) or via patents that are listed on the patent register specifically in order to deter or initiate litigation.

We identified 82 patents, granted over a period of 20 years, associated with the two drugs. Together, the patents had a 50 year cumulative term of patent protection. As shown in Figure 7a, the time course and duration of patent protection were sigmoidal, similar to the averaged data in Figure 5a. Data are given for the first NCE patent (●) and all subsequent patents (●) identified using the methodology described supra. The priority dates for the first and final patent were 1978 and 2005, respectively. Therefore, the period of hypothetical patent protection on the omeprazole group ran from 1975 to about 2025. In comparison, the first NOC for omeprazole (Losec®) was granted on June 13, 1989, yielding a regulatory gap of close to 10 years. Of 82 patents that were deemed relevant to omeprazole, 22, or 27% of all relevant patents, were listed on the patent register. If not listed on the register at some future point in time, the remaining 73% were deemed to function as blocking patents or fodder for future patent listing efforts. As noted supra, patents could be listed on more than one drug product provided they are legally relevant to the marketed product. This is reflected in the fact that the 22 patents were the subject of 75 individual legal determinations (many of which aggregated in a single trial).

All 22 listed patents have or continue to be disputed at trial in some form or another. This is shown in Figure 7b, which illustrates listed and litigated patents (●) and the timing and duration of ongoing (➞) and final (—) litigation. Litigation over 15 of the 22 patents lasted in excess of 2 years, with 14 final trial decisions to date. (Some patents were litigated multiple times, as indicated infra.) Final decisions were at the Federal Court of Canada, Federal Court of Appeal, or Supreme Court of Canada. As might be expected with so many patents being litigated multiple times, decisions on the merits were not harmonious from one decision to the next.[120] Indeed, there were numerous instances (n=11) where a court at one level decided that patents were invalid or not infringed with one set of litigants, while a different court at the same level decided that the same patents were valid and infringed with different litigants. In addition to litigation under the NOC Regulations, there were also 3 related patent infringement actions involving listed patents, one of which is ongoing (data not shown).

Figure 7 does not include data relating to individual trials. While this would have provided a better sense of just how extensive the litigation was

120. Bouchard, *PHOSITA*, *supra* note 73.

over these two drugs, it would have complicated the figure unnecessarily. For example, over the period 1993–2009, there were 61 separate trials on 22 listed patents, including 310 motions (mean=5.08 per trial) and 25 final trial decisions. Of final decisions, 14 were appealed to the Federal Court of Appeal and 8 went on to the Supreme Court of Canada. Litigation occurred over a term of sixteen years, essentially from the time the linkage regulations came into force in 1993 until the present. Four trials on 12 patents are currently ongoing.

Given that the NDS patent expired in 1999, extended patent protection on omeprazole has been ongoing for at least 10 years. But this does not necessarily equate to a decade of prohibited generic entry under the linkage regulations, owing to the requirement that generics must first obtain approval for market entry themselves *and* demonstrate in litigation that all relevant patents are invalid or not infringed by their product.[121] Of 25 final decisions levied by the courts, there were 13 cases where patents listed on the register were judged to be invalid or not infringed. The average date of the first automatic injunction for all litigants was February 2001. This represented the date on which drug approvals granted, or to be granted, to generic firms were "put on hold." The average date on which the group of 13 trials ended, and thus the date of "reactivation" of average generic approval was December 2003. Therefore, litigation over patents relating to Losec® and Nexium® resulted in a delay of market entry of close to three (2.83) years for the group. According to IMS Health,[122] sales of the two drugs in drugstores and hospitals over the same time frame were CN $1.4 billion. In comparison, total spending on prescription pharmaceuticals rose from CN $11.7 billion in 2001 to CN $17.97 billion in 2004,[123] representing an increase of 92%. This includes an increase in out-of-pocket consumer spending from CN $2.56 billion to CN $3.36 bil-

121. Merck Frosst Canada Ltd. v. Apotex Inc., [2009] F.C.A. 187 (Can.); Apotex Inc. v. Merck Frosst Canada Inc., [1998] 2 S.C.R 193 (Can.).

122. INTERCONTINENTAL MARKETING SERVICES HEALTH INC., 2003 ANNUAL REPORT TO SHAREHOLDERS (2003), http://www.imshealth.com/portal/site/imshealth; INTERCONTINENTAL MARKETING SERVICES HEALTH INC., 2002 ANNUAL REPORT TO SHAREHOLDERS (2002), http://media.corporate-ir.net/media_files/NYS/RX/reports/ar2002.pdf; INTERCONTINENTAL MARKETING SERVICES HEALTH INC., 2001 ANNUAL REPORT TO SHAREHOLDERS (2001), http://www.imshealth.com/portal/site/imshealth; *see also*, INTERCONTINENTAL MARKETING SERVICES HEALTH INC., CANADIAN PHARMACEUTICAL INDUSTRY REVIEW 2001 (on file with author); INTERCONTINENTAL MARKETING SERVICES HEALTH INC., CANADIAN PHARMACEUTICAL INDUSTRY REVIEW 2002 (on file with author); INTERCONTINENTAL MARKETING SERVICES HEALTH INC., CANADIAN PHARMACEUTICAL INDUSTRY REVIEW 2003 (on file with author).

123. CAN. INST. FOR HEALTH INFO., *supra* note 8. Note, the 2008 value was forecasted by the report, and is not an actual value.

lion. It is reasonable however to speculate that 'but for' the existence of the linkage regime that generic entry may have occurred closer to expiry of the NCE patent, with an accordingly shorter period of delayed entry. Either way, the linkage regulations regime has proved to be a highly effective mechanism for extending market monopolies on profitable pharmaceuticals.

D. LIMITATIONS

The strength of conclusions from our pilot study is tempered by two limiting factors. The first is that the time frame for the drug approval study is smaller (2001–2008) than that for the patenting (1978–2008) and patent listing (1993–2008) studies. This owes to the fact that our initial work on drug approval was done prior to undertaking the patent study. The year 2001 was chosen as our starting point in the drug approval study because substantial amendments to Canadian drug regulation were made at this time that affected both the mechanisms and speed of approval.[124] It will therefore be important for future work to include approval data from before the domestic linkage regulations came into force in 1993.

The second, and related, limitation is that the approval data set was for 608 drugs while our pilot study on drug patenting and linkage regulations was only for 16 drugs. For reasons given in Part II: Methods, this made good sense for the pilot study. We attempted to extrapolate the approval data back in time. However, given the yearly scatter in the data set and resulting confidence levels, this was not feasible. We obtain some assurance from the consistent nature of the daily and monthly scatter of approval data described in Figure 2. More importantly, we have now increased our data set to 95 of 608 approved drugs between 2001 and 2008 in a follow-up study. The results (data not shown) indicate that all major patterns for drug patenting and patent listing shown in Figures 4–7 are repeated not just for the entire 'most profitable' data set, but for three different sub-groups (most profitable, n=33; NOC/c, n=22; Priority Review, n=46). In particular, there was no substantial difference in the patenting data in Figures 4a–4d (n=16) and the 2-fold larger data set of most profitable drugs in the expanded study (n=33). Even so, future research must complete the patenting data for not only the 608 drugs approved during the period 2001–2008, but also for the broader drug ap-

124. HEALTH CANADA, STAKEHOLDER WORKSHOP, *supra* note 71, at 6 (explaining that the objectives of the 2001 regulations were to "[s]horten application review times without endangering health and safety; [i]mprove safety mechanisms for research subjects; [r]egulator to be more involved in clinical trial monitoring and follow-up; [r]emove obstacles to additional R&D; [i]mprove access to innovative therapies and advice from Canadian physicians with research experience").

proval data as it grows to encompass and back-date the coming into force of the linkage regulations in 1993 and beyond.

IV. DISCUSSION

A. TRENDS IN GLOBAL DRUG DEVELOPMENT

Data in Figure 1 demonstrate that the number of "new" drug approvals is decreasing significantly over time, while the number of follow-on approvals is increasing. Cumulative data in Figure 3 show that the number of truly innovative drug products is vanishingly small (1.23% of total and 1.87% of brand name approvals) over the eight-year test period. In general, our qualitative findings relating to pharmaceutical innovation parallel those observed in other jurisdictions.[125] That is, the multinational pharmaceutical industry is leaning away from breakthrough drug development towards less innovative products referred to variously as follow-on, incremental, supplemental, line extension, me too, and bioequivalent drugs.

While our data do not speak directly to claims that diminished innovation is due to the loss of "low hanging fruit"[126] or to the spiraling costs of drug development,[127] the data regarding the nexus between drug approval and patenting provide a third plausible explanation for the diminution of breakthrough product development. The results shown in Figures 1–7 suggest that innovation policy and drug regulation contingent on IPR rights can profoundly shape the rate and direction of innovative activity by multinational pharmaceutical firms antecedently, towards incentives provided for by law and away from truly breakthrough products under conditions where the two do not necessarily coincide.

Depending on the source and degree of industry affiliation, published de-

125. *See, e.g.*, NAT'L INST. FOR HEALTH CARE MGMT., CHANGING PATTERNS OF PHARMACEUTICAL INNOVATION 7 (2002); Domenico Motola et al., *An Update on the First Decade of the European Centralized Procedure: How Many Innovative Drugs*, 62 BRIT. J. OF CLINICAL PHARMACOLOGY 610 (2006); Editorial, *European and French Pharmaceutical Market Assessed by Prescrire in 2005: Mainly Bogus Innovation*, 30 FARMACIA HOSPITALARIA 68 (2006); 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*, 61 SOC. SCI. & MED. 881 (2005); *Drugs in 2001*, *supra* note 17; Kenneth I. Kaitin et al., *Therapeutic Ratings and End-of-Phase II Conferences: Initiatives To Accelerate the Availability of Important New Drugs*, 31 J. CLINICAL PHARMACOLOGY 17 (1991); *New Medicines in 2007: Regulatory Agencies and Policy Makers Leave Public Health in the Hands of the Pharmaceutical Industry*, 17 PRESCRIRE INT'L 78 (2008).

126. Fredric J. Cohen, *Macro Trends in Pharmaceutical Innovation*, 4 NATURE REVS. DRUG DISCOVERY 78, 82 (2005).

127. *See generally* Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003).

finitions of what constitutes an "innovative drug" vary considerably, from as low a threshold as simply containing an NAS,[128] to the slightly more stringent requirements of either being directed to FIC therapies[129] (irrespective of whether approval is directed to a new or follow-on drug) or to follow-on drugs that nevertheless undergo Priority Review.[130] However, merely containing an NAS is an insufficient basis for designating a drug as pioneering or strongly innovative because there is ample room in the definition for minor changes to previously approved medical ingredients, including salts, esters, solvates, polymorphs, and enantiomers. A similar conclusion applies to drugs that are only directed to FIC therapies, as these can also be follow-on versions of previously marketed products containing slightly modified medical ingredients or directed to new uses within a therapeutic class. Moreover, where Priority Review need only be directed to drugs demonstrating moderate clinical improvement over existing therapies, it is also an insufficient proxy for strong innovation. A more reasonable definition is that truly pioneering drugs are those that are approved via the new drug approval pathway (NDS), contain an NAS or NCE, undergo some form of Priority Review, and are directed to a FIC therapy.[131] Only in combination do these requirements approach a reasonable definition for a truly breakthrough technology.

Regulatory agencies in North America have previously attempted to derive innovation indices for pharmaceuticals. For example, in 2000, the Canadian Patented Medicines Prices Review Board[132] released data to the effect that of drugs approved between 1996–2000, 44.8% were line extensions and 49.6% were new versions of marketed drugs with moderate, little, or no improvement. Only 5.5% of all drugs approved represented a substantial therapeutic advance. These results parallel data from a large-scale study of innovation in the French prescription drug market demonstrating that of drugs approved over the term 1981–2001, the most innovative drugs represented only 3% of total approvals, while drugs with some important therapeutic gain and those with little to no therapeutic gain represented 8% and 89% of total approvals, respectively.[133]

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128. J. D. Kleinke, *Commentary: Much Ado About a Good Thing*, 325 BRIT. MED. J. 1168 (2002).

129. Cohen, *Macro trends in pharmaceutical innovation*, *supra* note 126; COMM. ON KNOWLEDGE ASSESSMENT, NAT'L RESEARCH COUNCIL, PROSPECTUS FOR NATIONAL KNOWLEDGE ASSESSMENT (1996).

130. NAT'L INST FOR HEALTH CARE MGMT., *supra* note 125.

131. *Id.*

132. PATENTED MEDICINE PRICES REVIEW BOARD, ANNUAL REPORT 2000 (2001), *available at* http://www.pmprb-cepmb.gc.ca/English/View.asp?x=113&mp=91.

133. *Drugs in 2001*, *supra* note 17, at 59; *see also New Medicines in 2007*, *supra* note 128, at

For the United States, Kaitin et al. reported data from an analysis of drugs approved by the FDA between 1978–1989 that were rated by the agency as having an important therapeutic gain, a modest gain, and little to no gain. [134] Only NCEs which excluded salts, esters, and other dosage forms of previously approved drugs were studied. The authors found that only 14.7% of approvals had the strongest innovation rating, whereas 34.5% and 49.5% were deemed modestly or weakly innovative. A more recent study by the NIHCM[135] demonstrated that of all drugs approved by the FDA during 1989–2000, 15%, 28%, and 57% were deemed to be the "most innovative" (NCE plus Priority Review), "moderately innovative" (follow-on plus Priority Review), and "modestly innovative"(follow-on), respectively.

As in Figures 1a and 1b, in the NIHCM and French studies, approvals for standard follow-on drugs increased steeply over the test periods, while data for the most innovative drugs remained flat over time. The fact that the values of 14.7% and 15% from the Kaitin and NIHCM studies represent NCEs with important therapeutic gain or drugs approved via the NDS stream, rather than drugs also undergoing Priority Review and directed to FIC therapies, suggests that the number of truly breakthrough drugs in these studies was more in line with data in Figures 1–3. With the exception of the French study, each of these indices were reported shortly after policy initiatives impacting drug development came into force, such as linkage regulations in the United States and Canada, the consolidation of U.S. patent appeals courts, and legislation facilitating technology transfer and commercialization via strong IPR rights.[136]

B. ROLE OF DRUG PATENTING AND LINKAGE REGULATIONS

Despite potential weaknesses in the empirical underpinnings of the innovation indices noted supra, it is of interest that there has never developed a parallel empirical literature relating to the social benefits of public health

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78–82. Note that the 2001 French study included new drugs and also new indications for existing drugs already on the market. Moreover, generic drugs were rated as no improvement over existing drugs. For discussion of the 2000 Canadian and 2001 French studies in the context of the Canadian pharmaceutical marketplace see generally Lexchin, *supra* note 17.

134. Kaitin et al., *supra* note 125, at 17–24.

135. NAT'L INST. FOR HEALTH CARE MGMT., *supra* note 125, at 8.

136. Jaffe, *supra* note 94 (discussing the pros and cons of arguments favoring the stimulation of innovation through provision of strong patent rights); Bhaven N. Sampat, *Patenting and US Academic Research in the 20th Century: The World Before and After Bayh-Dole*, 35 RES. POL'Y 772 (2006) (reviewing policy, legislative, and court reforms intended to facilitate commercialization of innovative products, including via strong intellectual property rights); Bouchard, *supra* note 61 (discussing the balancing of private intellectual property rights and publicly funded research in producing and commercializing innovative medical products).

and/or innovation policy that is strongly contingent on IPR rights[137]or that comprises a regulatory preference for incremental innovation. The social benefits of innovation are raised under the linkage regulations regime through the terms of the traditional patent bargain. This refers to the grant of a limited monopoly in exchange for public disclosure of socially valuable knowledge.[138] In a public health context where drug approval and drug patenting are linked, the essence of the patent bargain may be viewed as the exchange of extended patent protection for a socially beneficial level of pharmaceutical innovation. Thus, the public expects, and should expect, something of substantial social value in exchange for extended patent protection and monopoly pricing. In other words, the empirical or other data should support a strong legal and functional nexus between public health policy and patent policy.

Undue extension of patent protection for poorly innovative drugs via linkage regulations is similar in manner to so-called "weak" patents. Weak patents are those that provide poor levels of innovation over relevant prior art.[139] Leading courts have consistently held that patents of this nature stifle innovation,[140] chill competition,[141] encroach on the legal mandate of promoting the progress of science and useful arts,[142] and encourage inefficient transfers of wealth.[143] Relevant to the pharmaceutical market, weak patents hijack the IPR rights landscape[144] and allow patentees to extract unwarranted monopoly rents when they would otherwise receive nothing for non-inventive disclosures.[145] Policies underpinning patent protection must be sufficiently worthwhile to the public to warrant the restrictive effect of the patent mo-

137. Mazzoleni & Nelson, *supra* note 94; Pavitt, *supra* note 97.

138. *See, e.g.*, KSR Int'l v. Teleflex, Inc., 550 U.S. 398, 419 (2007); Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 17–18 (1966); Whirlpool Corp. v. Camco Inc., [2000] 2 S.C.R. 1067, ¶ 37 (Can.); *see also* Ron A. Bouchard, KSR v. Teleflex *Part 1: Impact of U.S Supreme Court Patent Law on Canadian Intellectual Property and Regulatory Rights Landscape*, 15 HEALTH L.J. 221 (2007).

139. *KSR Int'l*, 550 U.S at 419.

140. Hotchkiss v. Greenwood, 52 U.S. 248 (1851).

141. Whirlpool, 2 S.C.R. 1067; Free World Trust v. Electro Sante Inc., [2000] 2 S.C.R. 1024 (Can.); Royal Typewriter Co. v. Remington Rand, Inc., 168 F.2d 691 (2d Cir. 1948).

142. *KSR Int'l*, 550 U.S. at 419.

143. Anita Varma & David Abraham, *DNA is Different: Legal Obviousness and the Balance Between Biotech Inventors and the Market*, 9 HARV. J.L. & TECH. 53, 55 (1996). For general discussion of the relevance of weak patents to innovation, see also Glynn S. Lunney, Jr., *E-Obviousness*, 7 MICH. TELECOMM. & TECH. L. R. 363 (2001) and Bouchard, *PHOSITA*, *supra* note 73.

144. *See Royal Typewriter Co.* 168 F.2d at 693–94.

145. *See* Lunney, *supra* note 146, at 384.

nopoly,[146] and weak pharmaceutical patents in particular have been held to offend the public interest.[147]

The applicability of jurisprudence relating to weak patents may be particularly relevant to linkage regulations owing to two considerations that do not apply to other industries, technology-based or otherwise. The first is that the weak relevance standard for listing, which as discussed supra, provides a very broad target for patentees when aiming for the automatic injunction under both U.S. and Canadian linkage regulations.[148] This injunction, an earlier form of which has been referred to as "Draconian",[149] prevents generic firms from market entry until all patents on the register are proved in litigation to be invalid or not infringed.[150] The second is the empirical observation in both jurisdictions that litigation on the merits of contested patents under linkage regulations results in decisions where 75% of listed patents are deemed by the courts to be either invalid or not infringed by generic products.[151] It is reasonable to speculate that the administrative costs of prolonged litigation under linkage regulations are passed on to consumers in the form of extended monopoly pricing and other rent seeking behaviors.[152]

A linkage regulation regime that provides patent protection on poorly innovative drugs that extends well beyond the term of originating patents, not only has the potential to debilitate the patent system in the short term,[153] but

146. Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 11 (1966).

147. *See, e.g.*, R. v. Nova Scotia Pharm. Soc'y, [1992] 2 S.C.R. 606 (Can.); Comm'n of Patents v. Farbwerke Hoechst Aktiengesellschaft, [1964] S.C.R. 49, 56 (Can.).

148. Caffrey & Rotter, *supra* note 84; Hore, *supra* note 73. For a detailed discussion of the standard for relevance, see Regulations Amending the Food and Drug Regulations (Data Protection), Regulatory Impact Analysis Statement, 140 C. Gaz. pt. II, at 1495–1502 (2006), *available at* http://www.gazette.gc.ca/archives/p2/2006/2006-10-18/pdf/g2-14021.pdf.

149. Merck Frosst Can. Inc. v. Canada, [1998] 2 S.C.R 193 ¶ 33 (Can.). This passage has been cited by the court in later decisions. *See, e.g.*, AstraZeneca Can., Inc. v. Canada, [2006] S.C.R. 560, 2006 SCC 52 ¶ 17 (Can.); Bristol-Myers Squibb Co. v. Canada, [2005] 1 S.C.R. 533 SCC 26 ¶¶ 24, 146 (Can.).

150. *Id.*

151. FED. TRADE COMM'N, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY (2002), http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf [hereinafter FTC 2002]; *see* ED HORE, PATENTLY ABSURD: EVERGREENING OF PHARMACUETICAL PATENT PROTECTION UNDER THE PATENTED MEDICINES (NOTICE OF COMPLIANCE) REGULATIONS OF CANADA'S PATENT ACT 5, 11 (2004) http://www.canadiangenerics.ca/en/news/docs/patently_absurd_04.pdf (discussing data in the context of U.S. and Canadian linkage); Caffrey & Rotter, *supra* note 84, at 13–14.

152. *See* BOLDRIN & LEVINE, *supra* note 97, at 260–265 (discussing generally rent-seeking through patenting of follow-on drugs).

153. *See* Whirlpool Corp. v. Camco Inc., [2000] 2 S.C.R. 1067, ¶ 37 (Can.) (arguing that extending patent protections with follow on patents to obvious variations is counter to the patent bargain); Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 17–18 (1966) (holding

also to weaken pharmaceutical innovation in the long run. Innovation is weakened because the combination of weak relevance requirements and automatic injunctions takes patent protection to a point near its logical extreme. The data reported here suggest that if linkage regimes provide fertile grounds for firms to compete at a lower level of innovation, they also discourage firms from innovating at a level of competition that would provide the greatest benefit to society.

This dilemma can be illustrated by a comparison of data in Figures 3 and 5. On the one hand, Figure 3 demonstrates that a very small fraction of drugs approved by regulators over the 8 year test period could be considered truly breakthrough in nature. This includes drugs approved via the NDS stream (16%), those containing an NAS (6.1%), total NDS and SNDS drugs directed to FIC therapies (6.5%), those that underwent one of two pathways for expedited review (5.3%), and those that met the most stringent requirements for breakthrough products (1.23%). On the other hand, Figure 5 illustrates that patent protection under linkage regulations does not discriminate between poorly or strongly innovative drugs. It offers broad and long-lasting IPR rights to pharmaceutical firms regardless of the types of products being introduced into the marketplace. This is particularly relevant for follow-on drug products, which are recognized to entail lower risks and costs to pharmaceutical firms.[154] As suggested by data in Figures 1c, 6b, and elsewhere,[155] the evolution toward a lifecycle-based regulatory approach to drug approval will likely do little to affect the rate and direction of innovative activity by firms absent shifts in legal incentives for breakthrough and follow-on drug development.

The data in Figures 4–7 further support discordance between the basket of IPR rights incentives for innovation and resulting product development. For example, the close temporal relationship between drug approval and patent listing in Figure 4d and the strong convergence in Figure 4a of patent grant and patent listing following linkage regulations coming into force provide evidence that patent listing evolved into a more effective target, and thus a better proxy, for drug approval than drug patenting per se once the linkage regime came into effect. Other evidence for this conclusion comes from data in Figure 6, which demonstrate that steep time-dependent changes in drug patenting, patent listing, and the evolution toward lifecycle regulation appeared to have occurred independently of concomitant trends for new and follow-on drug approvals. The outcome of this dynamic, supported by aver-

that patents on obvious variations of known objects are invalid).

154. Cohen, *supra* note 126, at 79.

155. Sawicka & Bouchard, *supra* note 35.

aged data for sixteen drugs (Figure 5) and the single example of omeprazole (Figure 7), is that when given the opportunity, pharmaceutical firms will leverage government policy and regulation in order to maintain market share for drugs coming off patent instead of developing new blockbuster drugs. The results are not dissimilar to studies of complex political systems, where "yardsticks" designed to measure progress reorient behavior narrowly towards fulfillment of yardstick metrics.[156] The implication of this scenario is that firms are aiming ex ante at legal targets which provide the most return on investment rather than the most benefit to the public.

C. CONVERGENCE OF ECONOMIC AND PUBLIC HEALTH POLICY

The data reported here challenge two key assumptions that have underpinned public health policy and economic/industrial policy in industrialized nations for at least the past half century. The first is that strong IPR rights protection is essential to motivate and increase the amount of innovation that occurs in the economy. The second is that public health goals can best be met by encouraging innovation in private industry, essentially by merging public health goals with industrial development goals, buttressed by the IPR rights regime. Importantly, our findings do not indicate abnormal behavior by pharmaceutical companies, but rather failure of government policy and regulations to produce a specifically desired effect, namely, the increased production of truly innovative drugs. It is entirely understandable that pharmaceutical firms avail themselves of regulatory incentives allowing product evergreening after the original patent has expired where it maximizes the benefit and minimizes the risk to shareholders.[157]

Our findings suggest that blending of industrial and health policy goals may be ineffective and possibly counterproductive in terms of public health outcomes. They also suggest that although new lifecycle regulatory regimes have great potential to increase the efficiency of public health provision by

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156. *See generally* ROBERT JERVIS, SYSTEM EFFECTS: COMPLEXITY IN POLITICAL AND SOCIAL LIFE (1997).

157. AstraZeneca Can., Inc. v. Canada, [2006] S.C.R. 560, 2006 SCC 52 ¶ 39 (Can.). Discussing the "general" relevance requirement articulated by the Federal Court of Appeal in *Eli Lilly Canada Inc. v. Canada* [2003] FCA 24, Justice Binnie stated,

> Given the evident (and entirely understandable) commercial strategy of the innovative drug companies to evergreen their products by adding bells and whistles to a pioneering product even after the original patent for that pioneering product has expired, the decision of the Federal Court of Appeal would reward evergreening even if the generic manufacturer (and thus the public) does not thereby derive any benefit from the subsequently listed patents.

Id.

placing new remedies in clinical environments sooner, the efficacy of this approach can be weakened through inadequate monitoring and supervision, such that pharmaceutical firms perceive a higher incentive to exploit existing patented technologies in new ways rather than increasing the flow of new technologies. At a more general level, the data lend empirical support to an emerging consensus that, in many circumstances, IPR rights may be an inhibitor of innovation.

Although our study was based on domestic Canadian data, we argue that the results are significant within the global context of drug regulatory reform and innovation policy. First, efforts have been underway for some time to harmonize the goals and mechanisms of drug regulation globally. Second, in most developed nations, university-based translational research, firm research and development activities, and national science and technology policy are closely integrated and likewise mirror one another. Third, qualitative trends in approval of new and follow-on drugs track one another fairly closely in most major jurisdictions, and the drug patents that we analyzed represent the most profitable drugs not only in Canada, but also in U.S. and E.U. markets. Given that a small number of multinational pharmaceutical corporations are responsible for drug innovation globally[158] and are doing so increasingly in partnership with drug regulators,[159] it is reasonable to speculate that drug development and regulation in OECD economies is steadily converging upon a risk management philosophy whereby critical benefit-risk calculations are made not only for drug approval, but also for drug development.

We conclude that policy and legislative incentives designed to stimulate innovation in the pharmaceutical industry have had the opposite effect, and that shifting to a lifecycle regulatory model is unlikely to alter this scenario absent effort to balance legal and regulatory incentives for breakthrough and follow-on drug development. Our findings do not suggest abnormal behavior by pharmaceutical firms, but rather a failure of policy incentives intended to induce the desired result.[160]

158. BOLDRIN & LEVINE, *supra* note 97, at 241–42.

159. *See generally* Mary E. Wiktorowicz, *Emergent Patterns in the Regulation of Pharmaceuticals: Institutions and Interests in the United States, Canada, Britain, and France*, 28 J. HEALTH POL., POL'Y & L. 615 (2003).

160. *See* Barry Bozeman & Daniel Sarewitz, *Public Values and Public Failure in US Science Policy*, 32 SCI. AND PUB. POL'Y 119 (2005); Barry Bozeman, *Public Value Failure: When Efficient Markets May Not Do*, 62 PUB. ADMIN. REV. 145 (2002); John D. Sterman, *All Models Are Wrong: Reflections on Becoming a Systems Scientist*, 18 SYS. DYNAMICS REV. 501 (2002).

D. ANALYTICAL MODEL: PHARMACEUTICALS AND THE ECOLOGY OF INNOVATION

In this Article, we describe qualitatively and quantitatively various elements of the legal landscape governing biomedical innovation in a way that indicates that it functions as a strongly networked *innovation ecology*. We have referred to this ecology in previous work as a regulated Therapeutic Product Lifecycle (rTPL).[161] A highly simplified rTPL diagram is shown in Figure 8, which represents the lifecycle of therapeutic product development and regulation as a system ecology where the "whole is greater than the sum of its parts." Here, innovation is not depicted as a linear "pipeline," or process, moving from basic medical research in universities to applied research in firms, and then on to commercialized products.[162] Rather, the grouping of network nodes in the figure (arbitrarily but functionally connected) are interconnected and interdependent in an iterative manner over time. The functioning of the system cannot be understood from analysis of the properties of individual nodes.[163] Important for the present study, strongly altering the function of one element in the system, in this case the basket of IPR rights intended to stimulate innovation, has the potential to alter the behavior of the entire system.[164]

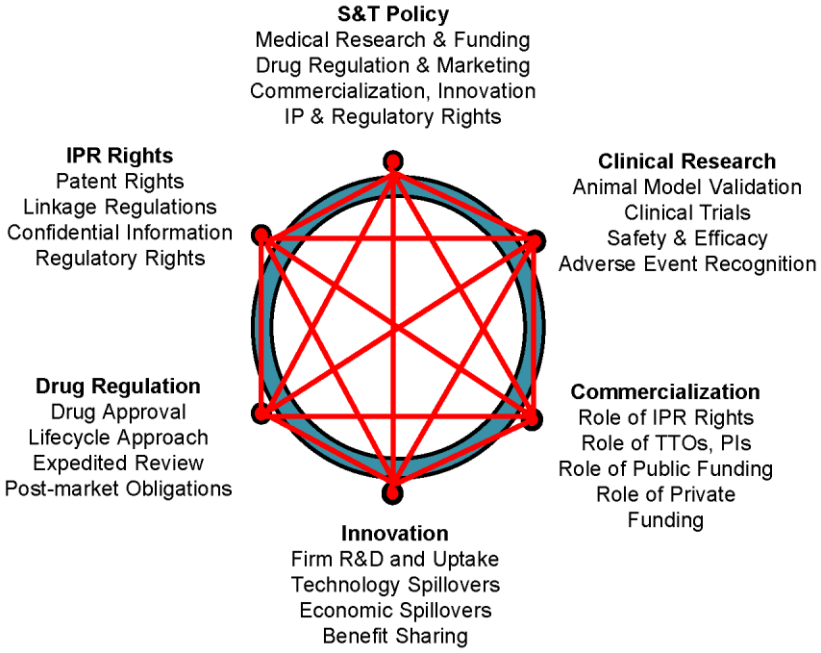
161. Ron A. Bouchard, *Reflections on the Value of Systems Models for Regulation of Medical Research and Product Development*, 17 HEALTH L. REV. 28 (2008) [hereinafter Bouchard, *Reflections*]; Sawicka & Bouchard, *supra* note 35.

162. Godin, *supra* note 90; STOKES, *supra* note 90.

163. Dean Rickles et al., *A Simple Guide to Chaos and Complexity*, 61 J. EPIDEMIOLOLOGY & COMMUNITY 933 (2007).

164. JOHN H. MILLER & SCOTT E. PAGE, COMPLEX ADAPTIVE SYSTEMS: AN INTRODUCTION TO COMPUTATIONAL MODELS OF SOCIAL LIFE 9 (2007).

Figure 8: Systems Model of a regulated Therapeutic Product Lifecycle (rTPL) Innovation Ecology



Innovation is represented as an iterative process over time involving several functional groupings, including national science and technology (S&T) policy, clinical research, university and firm commercialization, innovation by private firms, drug regulation by national governments, and intellectual property and regulatory (IPR) rights covering both drug submissions and marketed products. Large red nodes represent functional groupings, and include sub-functions enumerated in the figure. Red lines are multi-directional between nodes and sub-functions and are independent of time (acknowledging that the process generally moves clockwise).

It occurs to us that feedbacks between the various nodes in this innovation ecology are indicative of phenomena associated with complex adaptive systems, in which positive and negative feedback governs system learning, growth, and self-regulation.[165] In both biological and social systems, it has

165. Feedback interactions in complex systems have received increased attention in recent years. *See generally* ALBERT-LASZLO BARABASI, LINKED: HOW EVERYTHING IS CONNECTED TO EVERYTHING ELSE AND WHAT IT MEANS (Plume 2003) (investigating the role of feedback in biological and social networks, including corporations and living organisms, producing system fitness); JAMES GLEICK, CHAOS: MAKING A NEW SCIENCE (1988) (describing order and chaos generally and how complex systems balance the two through adaptation and positive and negative feedback loops); JOHN H. HOLLAND, ADAPTATION IN NATURAL AND ARTIFICIAL SYSTEMS (1992) (outlining the importance of adaptive mechanisms in natural and artificial systems to the growth and destruction of complex systems);

been demonstrated that strong positive feedback has the potential to move a system away from fitness or operational efficiency, even to the point of inducing the system to collapse.[166] In a complex system, 'order' can help the functioning of the system, but hinder it in others. For example, it has been observed in a range of natural and biological systems that imposition of too much order can yield a system that is inflexible.[167] Moreover, this inflexibility has the potential to move the system away from a state of fitness, in this case the production of breakthrough drugs. Once major patterns and institutions have been fully explored in a highly regulated system, the system may transition into what Kaufmann refers to as "detail mode"[168] where its further evolution is limited to modest improvements on increasingly optimized designs. Indeed, some evidence suggests that the more complicated the system, the more autonomous the agents in the system become, thus reducing the levels of control that it is possible to wield over them without stifling fitness or efficiency.[169]

JOHN H. HOLLAND, HIDDEN ORDER: HOW ADAPTATION BUILDS COMPLEXITY (1995) (discussing adaptation in complex adaptive systems and how order and disorder are often balanced at subtle levels in these systems); STEVEN JOHNSON, EMERGENCE: THE CONNECTED LIVES OF ANTS, BRAINS, CITIES, AND SOFTWARE (Scribner 2002) (discussing the characteristics of emergent systems, including the role of positive and negative feedback loops in governing de-centralized system growth and adaptation); STUART KAUFFMAN, AT HOME IN THE UNIVERSE: THE SEARCH FOR THE LAWS OF SELF-ORGANIZATION AND COMPLEXITY (Oxford University Press 1995) (investigating the conditions that give rise to the growth and destruction of complex adaptive systems and describing how optimal complex adaptive systems are balanced on the edge of chaos); GREGOIRE NICOLIS & ILYA PRIGOGINE, EXPLORING COMPLEXITY: AN INTRODUCTION (1990) (addressing the problem of complexity in using mathematical modeling and the role of essentially irreducible uncertainty in complex systems); M. MITCHELL WALDROP, COMPLEXITY: THE EMERGING SCIENCE AT THE EDGE OF ORDER AND CHAOS (Simon & Schuster 1992) (discussing the role of the interrelation and inter-dependence of players, including individuals and institutions, in complex adaptive systems and showing that systems of this nature are never in stasis, but rather always continually evolving); Brian W. Arthur, *Positive Feedbacks in the Economy*, 262 SCI. AM. 92, 92–99 (1990) (discussing the presence of feedback in producing order and simplicity even in the most complex economic systems).

166. *See, e.g.*, Robert M. May et al., *Complex Systems: Ecology for Bankers*, 451 NATURE 893 (2008) (explaining that catastrophic changes in financial systems can be attributed to its feedback mechanisms). For a look at the role of feedback in policy failure, see generally Bozeman & Sarewitz, *supra* note 160, (discussing how unintended consequences can result in "policy failure") and Sterman, *supra* note 160 (discussing the contribution of uncertainty and the unintended consequences of an action related to inadequate problem articulation). For a review of feedback in complex international political systems, see generally JERVIS, *supra* note 159; COMPLEXITY IN WORLD POLITICS: CONCEPTS AND METHODS OF A NEW PARADIGM (Neil E. Harrison ed., SUNY Press, 1997).

167. KAUFFMAN, *supra* note 165, at 26.

168. *Id.* at 14.

169. JOHNSON, *supra* note 165, at 186.

Based on the reasoning above, it would seem to be a reasonable conjecture that a complex adaptive innovation ecology, such as we have depicted as an rTPL, may then be one with a large degree of potential creativity and productivity balanced by an equal degree of uncertainty and instability and effected through positive and negative feedback loops, including those initiated by law. This discussion has potentially significant implications for the interpretation of existing pharmaceutical policy, regulation, and literature, including the data reported here. In our previous work on pharmaceutical innovation and litigation,[170] we suggested that regulatory preferences that do not respect the complex nature of the system they seek to regulate (including over-regulation masquerading as under-regulation) have the potential to harm the innovative outputs of the system. This result can be affected by either allowing undue capture of resources or benefits into the hands of discrete actors or through loss of innovative capacity relative to practical considerations of use, including those incentivized through regulatory preferences.

The model in Figure 8 envisions all steps in the innovation process as interdependent, particularly over the longer horizon.[171] At the 'beginning' of the process, national science and technology policies are negotiated and initiated to drive national innovation priorities.[172] These policies set the balance between economic and public health goals and expenditures.[173] The next point is represented by publicly funded medical research,[174] which policymakers now desire to be strongly 'translational' in nature and therefore underpinned by strong IPR rights.[175] The mid-point of the process is where clinical trial results become increasingly available, at which point firms identify attractive technologies and begin to layer more substantial IPR rights over them, particularly patent rights. These patent rights, and the various spin-out firms they can create (e.g. from technology transfer), then become metrics, which in turn are used to determine what constitutes effective and efficient national science and technology policies and practices.[176] Finally, we move

170. For general discussion of the problems inherent in linear legislative and jurisprudential models of pharmaceutical innovation and how they may be mitigated by systems models of innovation, see generally Ron A. Bouchard, KSR v. Teleflex *Part 2: Impact of U.S. Supreme Court Patent Law on Canadian and Global Systems-Based Innovation Ecologies*, 15 HEALTH L.J. 247 (2007) [hereinafter Bouchard, *Systems*]; Bouchard, *Reflections*, *supra* note 161; Bouchard, *PHOSITA*, *supra* note 73.

171. Arthur, *supra* note 93.

172. Bouchard, *Systems*, *supra* note 170 at 248–50; *see also* Bouchard & Sawicka, *supra* note 29, at 57–58.

173. Bouchard & Lemmens, *supra* note 87.

174. *See id.*; Bouchard, *supra* note 61.

175. *See id.* at 2–3.

176. For discussion of the failure of linear models of "basic" and "applied" research and

towards the perceived terminus of the process, where products are at or near the regulatory approval point and firms have identified targets for either novel breakthrough products or incremental innovations with strong evergreening potential.[177] At this point, and especially at later points in the rTPL, [178] linkage regulations and regulatory rights become dominant forms of IPR rights protection.[179] However, as noted earlier, the mid-point and end-point of the pharmaceutical innovation system are increasingly merging, as regulators move towards lifecycle regulatory models which allow for early or flexible departure of drugs prior to completion of tradition Phase 3 trials, with greater post-market surveillance. Moreover, both pharmaceutical, and more recently biotechnology, firms operating under the linkage regime can now layer IPR rights on products at all stages of development, including those about to come off patent, those in regulatory review, and those in development. Recent data[180] indicate that the linkage regime operating in conjunction with established patent law and the drug approval regime allows firms to produce a substantial number and array of patent classifications, which can in turn be used to list on the patent register in order to prohibit generic entry on older drugs and to support follow-on drug development submissions, thus further collapsing the drug development cycle. The present study therefore supports the need to extend and broaden the innovation analysis to include the entire landscape of interconnections between drug approval, patenting, and litigation, as well as the nexus between broader national science and technology policies and the effects thereof on the rate and direction of firm innovation.[181]

Schumpeter noted that innovations of different magnitudes tended to appear in cycles of varying lengths, geared largely to the rate at which advantages from innovations declined over time through increasing use and imita-

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development to account for the innovation process, see generally STOKES, *supra* note 90; Godin, *supra* note 90.

177. Bouchard, *Scientific Research*, *supra* note 73, at 13; Bouchard, *PHOSITA*, *supra* note 73, at 22–23.

178. For discussion of regulatory rights, how they relate to traditional food and drug law, and the points in the drug development cycle at which they come into play, see generally Caffrey and Rotter, *supra* note 84; Eisenberg, *supra* note 84; Hore, *supra* note 73; HORE, *supra* note 151.

179. Bouchard, *PHOSITA*, *supra* note 73, at 48; Bouchard & Sawicka, *supra* note 29, at 63–64.

180. Ron A. Bouchard et al., *Empirical Analysis of Drug Approval-Patenting Linkage for High Value Pharmaceuticals*, 8 NW. J. TECH. & INTELL. PROP. (forthcoming 2010).

181. Bouchard, *Systems*, *supra* note 170, at 258–62; Bouchard, *Reflections*, *supra* note 161, at 38–39.

tion.[182] For policies and regulations aimed at stimulating innovation, the risk is always that they may catch one of these cycles at the wrong moment, thus contributing more to the declining phase of an existing cycle than to the development phase of a new one. They may do this by damaging the incentives that drive new entrants, or by preserving practices that have become inefficient.[183] Clearly this applies to inefficient or ineffective regulatory policies that lead to increasingly poor performance as judged by the goals and objectives of policy-makers, in this case an increased supply of truly innovative remedies.

Based on data here and elsewhere,[184] we propose that the current lifecycle of pharmaceutical development *and* regulation may be nearing a point of exhaustion such as Schumpeter would have recognized. Evidence for this includes: a strongly increasing trend towards ever-smaller incremental innovation in the last decade (Figure 1); an increase of low level of innovation being supported by a combination of weak patents and linkage regulations (Figures 4–7); a decreasing number of truly breakthrough drugs as well as drugs containing NCEs and NASs (Figures 1 and 3); a substantial number of patents per drug (Figure 4); the fact that many patents under linkage regulations are either invalid or infringed when tested on the merits,[185] and the growth in both the scope and depth of IPR rights associated with poorly innovative drug products over the last 20 years.

As noted by many commentators, the basket of IPR rights afforded to pharmaceuticals has grown to encompass an astounding array of mechanisms, which may be interpreted as micro levels of order or detail as per the discussion supra. These include increased patent terms, decreased standards for obviousness, utility, and subject matter requirements for patenting, allowance for listing of weak patents via linkage regulations, the automatic stay provision barring generic entry, loss of compulsory licensing provisions, and the ever growing basket of regulatory rights associated with drug submis-

182. JOSEPH A. SCHUMPETER, BUSINESS CYCLES: A THEORETICAL, HISTORICAL AND STATISTICAL ANALYSIS OF THE CAPITALIST PROCESS (1939); *see also* Gert-Jan Hospers, *Joseph Schumpeter and His Legacy in Innovation Studies*, 18 KNOWLEDGE TECH. & POL'Y 20 (2005) (reviewing the relevance of Schumpeter's work for current innovation theory and practice).

183. *Id.* at 32.

184. For a review of cumulative empirical studies of pharmaceutical innovation and patenting, see BOLDRIN & LEVINE, *supra* note 97, particularly Chapter 8 ("Does Intellectual Property Increase Innovation?") and Chapter 9 ("The Pharmaceutical Industry").

185. *See, e.g.*, FTC 2002, *supra* note 151; Caffrey & Rotter, *supra* note 84; Valerie Junod, *Drug Marketing Exclusivity Under United States and European Union Law*, 59 FOOD & DRUG L.J. 479 (2004); Hore, *supra* note 73.

sions.[186] It is not just a coincidence that the basket of IPR rights attached to pharmaceutical products is growing in both scope and depth at a time when innovation is widely considered to be faltering.

Even if the current rTPL is not near the point of exhaustion, data such as those reported here should provide useful information for jurisdictions contemplating some form of linkage regulations or other types of linkages between public health and economic policies. In jurisdictions that maintain that IPR rights are integral to innovation, the results may offer an opportunity to correct or fine-tune existing policies underpinning innovation, including adjusting economic incentives in accordance with the degree of innovation and accompanying social benefits[187] based on a growing body of empirical data.[188]

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186. Regulations Amending the Food and Drug Regulations (Data Protection), Regulatory Impact Analysis Statement, 140 C. Gaz. pt. II, at 1495–1502 (2006), *available at* http://www.gazette.gc.ca/archives/p2/2006/2006-10-18/pdf/g2-14021.pdf (demonstrating that "regulatory rights," such as market data and pediatric exclusivity, add up to a term of market exclusivity in various jurisdictions ranging from 5.5 to 11.5 years and that this period of market exclusivity exists independent and alongside patent protection via traditional patent legislation and emerging linkage regulations.) While regulatory rights spread globally via provisions to this effect in TRIPS and other U.S.-based trade agreements, they have been the subject of increasing scrutiny recently, including within the United States. For example, Senator Bernie Sanders (I-VT) recently put forward an amendment to the health care reform bill that would eliminate data exclusivity where duplicating clinical trials involving human subjects violates Article 20 of the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human subjects pertaining to clinical trial ethics. James Love, *Senator Sanders Amendment 2858 Would Replace Data Exclusivity with Cost Sharing, If New Trials Violate Medical Ethics*, KNOWLEDGE ECOLOGY INT'L, Dec. 9, 2009, http://keionline.org/node/707.

187. Michael Abramowicz, *Perfecting Patent Prizes*, 56 VAND. L. REV. 115 (2003); Amitava Banerjee et al., *The Health Impact Fund: Incentives for Improving Access to Medicine*. 375 THE LANCET 166 (2010); Paul Grootendorst, *Patents, Public-Private Partnerships or Prizes: How Should We Support Pharmaceutical Innovation?* (Soc. & Econ. Dimensions of an Aging Population, Paper No. 250), *available at* http://socserv2.socsci.mcmaster.ca/~sedap/p/sedap250.pdf; Aidan Hollis, *Optional Rewards for New Drugs for Developing Countries*, (April 5, 2005) (unpublished manuscript, on file with the World Health Organization), *available at* www.who.int/entity/intellectualproperty/submissions/Submissions.AidanHollis.pdf; Aidan Hollis, *An Efficient Reward System for Pharmaceutical Innovation*, (Jan. 17, 2005) (unpublished manuscript, on file with the University of Calgary), *available at* http://econ.ucalgary.ca/fac-files/ah/drugprizes.pdf; Joseph Stiglitz, *Scrooge and Intellectual Property Rights: A medical prize fund could improve the financing of drug innovations*, 333 BRIT. MED. J. 1279 (2006).

188. For example, existing price control methodologies employed by governments (e.g., Patented Medical Prices Review Board of Canada) or insurers and other institutional payers may be modified to incorporate an "innovation index" factor such as that described in Figure 3d in their pricing algorithms. Prices could be increased or decreased in accordance with empirical assessment of whether approved drugs, when compared with existing drugs, are highly innovative (NDS+NAS+ER+FIC or NDS+NAS+FIC), moderately innovative (NDS+ER+NAS or NDS+NAS), less innovative (SNDS+ER+FIC or SNDS+FIC), poorly innovative (SNDS) or not innovative at all (ANDS; SANDS).