

Global Pharmaceutical Linkage Regulations: A Proposed Analytical Framework

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I. ABSTRACT

Prompt and affordable access to essential medicines is a component of almost all domestic and global public health models. As is now well known, the availability and costs of both brand and generic drugs is a function of traditional patent law incentives. Less known, however, is that generic entry is controlled increasingly through an emerging form of global intellectual property law referred to as “linkage regulations.” Linkage regulations tie generic drug approval, and thus access to essential medications, to existing drug patents through potentially long and costly litigation. The linkage regime is in the process of rapidly spreading worldwide through international free trade agreements. Even so, very little is known about how the regulations work in developed nations let alone how they impact on public health systems across international borders. The authors constitute a network of eleven health policy experts and practicing lawyers in nine countries including those with mature linkage regulations, those with new regulations, those without regulations but with practices that parallel linkage, and those where regulations are currently subject to intense public debate and litigation. Here, we propose a novel structure-function framework to conduct a comparative legal analysis of global pharmaceutical linkage, with the aim of obtaining critical information about the costs and benefits of tying pharmaceutical innovation and generic drug availability to drug patenting. A major goal of the research is to investigate the structural and functional aspects of global linkage regulations as they relate to drug availability, costs and expenditures on the one hand and incentives for innovation and protection of rights on the other. The structural and functional aspects we discuss here include: assessment in each jurisdiction of the original policy intent underpinning linkage; the manner in which public health policy and economic policy is perceived by governments and the courts to converge or diverge through linkage; the specific legal checks and balances designed specifically to maintain balance between the interests of brand and generic firms; the growing expansion of linkage beyond the drug approval-drug patenting nexus to encompass drug pricing and reimbursement; and the role of empirical studies to establish the legal legitimacy of linkage regulations. A second major goal of our work is to assist domestic and global governments and legal systems working with linkage regimes to balance the

production of new and innovative drugs with timely generic entry, and thus to lower public health costs and increase access to essential medicines.

II. EVOLUTION OF GLOBAL PHARMACEUTICAL LINKAGE

Prompt and affordable access to essential medicines is a significant component of most models of domestic and global public health and is central to the goal of ensuring value for money regarding drug costs and expenditures. The availability and costs of new and generic drugs is a function of traditional patent law incentives and emerging linkage regulations. Patent law is a well described,¹ if controversial,² policy lever for stimulating drug development.³ Linkage regulations tie generic drug availability to existing drug patents by connecting approval to the resolution of patent validity or infringement.⁴ This can result in long and costly litigation, the costs of which are ultimately borne by consumers.⁵

The patent system has been in operation for over 500 years, with early patent laws in Italy and the United Kingdom.⁶ By contrast, the linkage regime has only been in existence for about 25 years following passage of the Drug Price Competition and Patent Term Restoration Act (Hatch Waxman Act) in the United States⁷ and the Canadian Patented

¹ Kenneth Arrow, *Economic Welfare and the Allocation of Resources for Invention* (Rand Corporation, 1959); Kenneth Arrow, "Economic Welfare and the Allocation of Resources for Innovation" in Nelson, ed, *The Rate and Direction of Inventive Activity* (Universities-National Bureau, 1962) 609-626; Robert P. Merges & Richard R. Nelson, "On the complex economics of patent scope" (1990) 90 Colum. L. Rev. 839; Dan L. Burk & Mark A. Lemley, "Policy Levers in Patent Law" (2003) 89 Va. L. Rev. 157; David Vaver, *Intellectual Property Rights: Critical Concepts in Law* (Routledge, 2006). For an account of the relationship between patents and drug discovery, development and marketing from the earliest days of the industry to the present, see Graham Dutfield, *Intellectual Property Rights and the Life Science Industries: Past, Present and Future* (Singapore: World Scientific, 2009).

² Sheldon Krinsky, *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* (Lanham, MD: Rowman & Littlefield, 2003); Michele Boldrin & David K. Levine, *Against Intellectual Monopoly* (Cambridge University Press, New York, 2008); James Bessen & Michael J. Meurer, *Patent Failure: How Judges, Bureaucrats, and Lawyers Put Innovators at Risk* (Princeton: Princeton University Press, 2008); Adam Jaffe, "The U.S. Patent System in Transition: Policy Innovation and the Innovation Process" (2000) 29 Research Policy 531; Roberto Mazzoleni & Richard R. Nelson, "The Benefits and Costs of Strong Patent Protection: A Contribution to the Current Debate" (1998) 27 Research Policy 273.; Michele Boldrin & David K. Levine, "The Economics of Ideas and Intellectual Property" (2005) 102 Proceedings of the National Academy of Sciences of the United States of America 1252; Keith Pavitt, "National Policies for Technical Change: Where are the Increasing Returns to Economic Research?" (1996) 93 Proceedings of the National Academy of Sciences of the United States of America 126.

³ Bouchard, R.A., "Should Scientific Research in the Lead-Up to Invention Vitate Obviousness Under the Patented Medicines (Notice Of Compliance) Regulations: To Test or Not to Test?" (2007) 6(1) C.J.L.T. 1-27 [Bouchard, 2007a]; Bouchard, R.A., "Living Separate and Apart is Never Easy: Inventive Capacity of the PHOSITA as the Tie that Binds Obviousness and Inventiveness" (2007) 4(1) University of Ottawa Law & Technology Journal 1-57 [Bouchard, 2007b]; Bouchard, R.A., "KSR v. *Teleflex* Part 1: Impact of U.S. Supreme Court Patent Law on Canadian Intellectual Property and Regulatory Rights Landscape" (2008) 15(1) Health L. J. 222-246; Faunce, T.A & Lexchin J., "'Linkage' Pharmaceutical Evergreening in Canada and Australia" Australia and New Zealand Health Policy (2007) 4(1) at 8; Paul Jones, "KSR and the Supreme Court: The silence is deafening" (2008) 53 Antitrust Bulletin 849.

⁴ *Patented Medicines (Notice of Compliance) Regulations* amend. S.O.R. /93-133 (NOC Regulations). For review of Canadian linkage regulations, see: Edward Hore, "A Comparison of United States and Canadian Laws as They Affect Generic Pharmaceutical Market Entry" (2000) 55 Food & Drug L.J. 373; Lexchin J., "After compulsory licensing: Coming issues in Canadian pharmaceutical policy and politics" (1997) 40(1) Health Policy 69-80; Bouchard, R.A., "I'm Still Your Baby: Canada's Continuing Support of U.S. Linkage Regulations for Pharmaceuticals" (2011) 15(1) Marquette Intellectual Property Review 1-52 [Bouchard 2011]. Faunce refers to linkage as that between generic drug safety, quality and efficacy approval to the assessment of potential patent infringement: Tom Faunce, "Global Intellectual Property Protection for Innovative Pharmaceuticals: Challenges for Bioethics and Health Law" in B Bennett and GF Tomosy (eds.), *Globalisation and Health* (Springer, Dordrecht, 2006) 87-108. For the sake of simplicity, the term "linkage" is used in this article to refer to the nexus between drug approval and drug patenting.

⁵ Boldrin & Levine 2008.

⁶ Jean O. Lanjouw & William Jack. "Trading Up: How Much Should Poor Countries Pay to Support Pharmaceutical Innovation?" (2004) 4(3) Center for Global Development Brief 1-8.

⁷ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as

Medicines (Notice of Compliance) Regulations (NOC Regulations).⁸ In both originating jurisdictions, the linkage regime was brought in explicitly to balance the competing policy goals of stimulating the development of new and innovative drugs and facilitating the timely entry of generic drugs.⁹ Compared to the patent system, the linkage regime therefore represents a novel and emerging intellectual property paradigm for protecting pharmaceutical inventions.

Given the comparative youth of the pharmaceutical linkage regime, it is not surprising that empirical data are only now beginning to be reported on the impact of linking drug approval to drug patenting on the twin policy goals of encouraging the development of new drugs and the timely entry of generic competitors. This includes earlier qualitative studies of gaming the automatic stay and other provisions in the originating American and Canadian linkage regimes,¹⁰ as well as newer quantitative empirical studies of the performance and outputs of both systems over time.¹¹

Of growing interest from a global public health perspective, pharmaceutical linkage is no longer restricted to the North American context or solely to the drug approval-drug patenting nexus. Indeed, in 2010 we are witnessing the rapid spread of the linkage regime on a global level including to developing countries where access to generics is both of more significance and more problematic. This is due to a growing number of multilateral and bilateral Free Trade Agreements (FTAs) involving the United States.¹² Recent agreements

amended at 21 U.S.C. § 355 (2000)) (Hatch Waxman Act). For description of U.S. linkage laws, *see*: Gerald Mossinghoff, "Overview of the Hatch Waxman Act and its impact on the drug development process" (1999) 54 Food & Drug L. J. 187-194; 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," (2004) 9 Va. J.L. & Tech. 1, 4-7; Rebecca S. Eisenberg, "Patents, Product Exclusivity, and Information Dissemination: How Law Directs Biopharmaceutical Research and Development" (2003) 72 Fordham L. Rev. 477, 483; Jeremy Bulow, "The Gaming of Pharmaceutical Patents" (2003) National Bureau of Economic Research (NBER) Paper; Richard Epstein & Bruce Kuhlik, "Navigating the Anticommons for Pharmaceutical Patents: Steady the Course on Hatch Waxman" University of Chicago Law & Economics Working Paper No. 209 (2004); Mathew Avery, "Continuing Abuse of the Hatch Waxman Act by Pharmaceutical Patent Holders and the Failure of the 2003 Amendments" (2008) 60 Hastings L.J. 171.

⁸ Robert Tancer, "Foreign investment in North America and the Pharmaceutical Industry in Canada" (1997) 39(2) The International Executive 283-297; Christopher Scott Harrison, "Protection of Pharmaceuticals as Foreign Policy: The Canada-U.S. Trade Agreement and Bill C-22 Versus the North American Free Trade Agreement and Bill C-91", (2001) 26 N.C. Int'l L. & Com. Reg. 457-528. Edward Hore, "A Comparison of United States and Canadian Laws as They Affect Generic Pharmaceutical Market Entry" (2000) 55 Food & Drug L.J. 373.

⁹ Avery 2008; Bouchard 2011.

¹⁰ Federal Trade Commission 2002 Study, "Generic Drug Entry Prior to Patent Expiration: An FTC Study", online: Federal Trade Commission <<http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf>> [FTC Study 2002]; Caffrey 2003; Bulow 2003; Epstein and Kuhlik 2004; Avery 2008.

¹¹ Sawicka, M & Bouchard, R.A., "Empirical Analysis of Drug Approval Data 2001-2008: Are Canadian Pharmaceutical Players "Doing More With Less"?" (2009) 3(1) McGill Journal of Law & Health 49-84; Bouchard, R.A., *et al.*, "The *Pas de Deux* of Pharmaceutical Regulation and Innovation: Who's Leading Whom?" (2009) 24(3) Berkeley Tech. L. J. 1461-1522 [Bouchard 2009]; Bouchard, R.A., *et al.*, "Empirical Analysis of Drug Approval-Drug Patenting Linkage for High Value Pharmaceuticals" (2010) 8(2) Northwestern Journal of Technology & Intellectual Property 174-227 [Bouchard 2010]; Hemphill, S.C., Sampat, B., When do Generics Challenge Drug Patents. (2010) Columbia Law and Economics Working Paper No. 379. Online: <<http://ssrn.com/abstract=1640512>>; Hemphill, S.C. and Lemley, M. Earning Exclusivity: Generic Drug Incentives and the Hatch Waxman Act. Stanford Law and Economics Olin Working Paper No. 405, Columbia Law and Economics Working Paper No. 391. Online, <http://papers.ssrn.com/sol3/cf_dev/AbsByAuth.cfm?per_id=32215>.

¹² Carlos María Correa, "Bilateral free trade agreements and access to medicines" (2006) 84 Bulletin of the World Health Organization 399-404; Judit Rius Sanjuan, *Patent-Registration Linkage*, CPTech, 3 April 2006, online: CPTech <<http://www.cptech.org/publications/CPTechDPNo2Linkage.pdf>>; Finston Consulting, LLC. Overview on Patent Linkage. (7 August 2006) online: Finston Consulting, LLC. <<http://www.finstonconsulting.com/version03/files/Overview.pdf>>)UK Consulting Report).

include Trade Related Aspects of Intellectual Property Rights (TRIPS),¹³ as well as narrower agreements between the United States, Canada and Mexico,¹⁴ Australia¹⁵ and Korea,¹⁶ among others.¹⁷ The latter agreements require participating nations to incorporate linkage and other intellectual property provisions in their patent systems in exchange for preferential trade terms¹⁸ and are increasingly negotiated outside the purview of the World Trade Organization (WTO). As these provisions provide stronger intellectual property protection for drugs than provided for by TRIPS, they are referred to as “TRIPS-Plus”.¹⁹ The European Commission (E.C.) Pharmaceutical Enquiry recently reported several instances where member nations have attempted to institute pharmaceutical linkage regimes even though European Union law prohibits same.²⁰

The implications of pharmaceutical linkage to global public health are great. For example, recent work has shown that the linkage regime can extend cumulative patent terms for high value pharmaceuticals by as much as two-fold beyond that provided by the basic patent covering the compound.²¹ This is consistent with early predictions of the impact of linkage on cumulative market exclusivity by Schondelmeyer,²² based on his work with the originating U.S. regime.²³ An additional concern is that the extension of market exclusivity on brand drugs (and thus prolonged monopoly pricing) occurs even though up to 50-75% of patents challenged may be invalid or not infringed by the generic equivalent.²⁴ This creates a conflicting system in which governments with linkage regimes that limit the timely appearance of generics also depend on these firms to produce cost savings and limit the growth in pharmaceutical expenditures. A related issue is that costs of prolonged litigation are passed on to consumers,²⁵ with differential costs to governments and the public in

¹³ *Agreement on Trade Related Aspects of Intellectual Property (TRIPS) 1994*, 30 October 1994, 58 U.N.T.S. 187, Can. T.S. 1947 No. 27 (negotiated as part of the Uruguay Round (1986-1994) of the World Trade Organization’s General Agreement on Tariffs and Trade [GATT]).

¹⁴ North American Free Trade Agreement Between the Government of Canada, the Government of Mexico, and the Government of the United States, 17 December 1992, Can. T.S. 1994 No. 2, 32 I.L.M. 289 (entered into force 1 January 1994).

¹⁵ H.R. 4759: United States-Australia Free Trade Agreement Implementation Act. online, <<http://www.govtrack.us/congress/bill.xpd?bill=h108-4759>>

¹⁶ Korea-U.S. Free Trade Agreement [KorUS FTA], signed June 30, 2007. online: Office of the United States Trade Representative <<http://www.ustr.gov/trade-agreements/free-trade-agreements/korus-fta>>

¹⁷ Correa 2006.

¹⁸ Faunce 2006; Faunce TA and Shats K., “Bilateral Trade Agreements as Drivers of National and Transnational Benefit From Health Technology Policy: Implications of Recent US Deals for Australian Negotiations with China and India” (2008) 62(2) *Australian Journal of International Affairs* 196-213.

¹⁹ Correa 2006.

²⁰ European Commission Pharmaceutical Sector Inquiry Final Report, 8 July 2009, at 23 [EC Pharmaceutical Sector Report]. This theme is developed extensively in the European Commission Pharmaceutical Sector Inquiry Preliminary Report, 28 November 2008 [EC Pharmaceutical Sector Preliminary Report], at pp. 14 and 113.

²¹ Bouchard 2009.

²² Dr. Stephen Schondelmeyer, a pharmacologist and health economist, gave evidence before the House of Commons to the effect that it is not the term of single patents that mattered most, but rather how patents add cumulatively to extend market exclusivity, a claim the government at the time vigorously denied. Compare testimony of Dr. Stephen Schondelmeyer (Professor, University of Minnesota) and Dr. Kay Dickson (Director General, Department of Industry, Science & Technology). Parliament of Canada, 33:7, *Minutes of Proceedings and Evidence of the Legislative Committee on Bill C-22*. (1 December 1992) 7:65-7:96 and 33:8 2 September 1992, 8:37-8:40.

²³ Lara J. Glasgow, “Stretching the Limits of Intellectual Property Rights: Has the Pharmaceutical Industry Gone Too Far?” (2001) 41 *Idea* 227, citing data from a U.S. study at note 27: The Gale Group, “Intellectual Property Rules: A Delicate Balancing Act for Drug Development” (2001) 23 *Chain Drug Review*. RX13.

²⁴ FTC 2002 Study; Hore 2004; Caffrey 2003. It should be noted, however, that these data are now somewhat old, and require updating in both the U.S. and Canada following amendments to the respective linkage regimes over the last half decade.

²⁵ Boldrin & Levine, 2008; Bulow, 2003.

accordance with their system of drug reimbursement,²⁶ public health,²⁷ public-private discourse,²⁸ and health equity.²⁹

Considerations such as the forgoing must be balanced against the widely accepted need for innovative drugs in developed and developing nations, the presumption of patent validity in nations with established patent legislation, and the idea in law that if the state grants a party an exclusive legal right, it cannot turn around and grant another party permission to encroach upon that right without just cause.³⁰

A related observation is that while the concept of pharmaceutical linkage is new compared to the patent system, there is already significant pressure to broaden it beyond drug approval to include linkage between patent rights and other regulatory aspects of drug approval and marketing.³¹ An expansive concept of linkage would differ significantly from the relatively discrete legal nexus between drug patents and the marketed products against which they are listed envisioned by the architects of linkage in the United States and Canada.³² For example, the E.C. Pharmaceutical Sector Inquiry³³ recently articulated a broad definition of pharmaceutical linkage, including linkage of patent status to formal legal proceedings between parties; patent settlements; as well as a wide range of interventions before national drug regulators, including those relating to market approval, drug pricing, and reimbursement.³⁴

²⁶ Colleen Flood, Mark Stabile & Carolyn Tuohy, eds. *Exploring Social Insurance: Can a Dose of Europe Cure Canadian Health Care Finance?* (Montreal: McGill-Queen's University Press, 2008).

²⁷ Philip J. Hiltz, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Alfred A. Knopf, 2003); Jerry Avorn, *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs* (New York: Alfred A. Knopf, 2004); Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What To Do About It* (New York: Random House, 2004); Jay S. Cohen, *Overdose: The Case Against the Drug Companies* (New York: Penguin, 2001); Ray Moynihan & Alan Cassels, *Selling Sickness: How the World's Biggest Pharmaceutical Companies Are Turning Us All Into Patients* (New York: Nation Books, 2005).

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

²⁹ Kevin Outterson, "Pharmaceutical Arbitrage: Balancing Access and Innovation in International Prescription Drug Markets" Yale Journal of Health Policy, Law and Ethics, December 2004; Kevin Outterson, "Should access to medicines and TRIPS flexibilities be limited to specific diseases?" (2008) 34(2-3) Am. J. L. & Med. 123-137; Trudo Lemmens, "Leopards in the Temple: Restoring Scientific Integrity to the Commercialized Research Scene" (2004) 32 J.L. Med. & Ethics 641; Trudo Lemmens, "Piercing the Veil of Corporate Secrecy about Clinical Trials" (2004) 34(5) Hastings Center Report 14; E. Richard Gold, "The Reach of Patent Law and Institutional Competence" (2004) 1 University of Ottawa Law & Technology Journal 263.

³⁰ Mark A. Lemley & Douglas Lichtman, "Rethinking Patent Law's Presumption of Validity" (2007) 60 Stan. L. Rev. 45.

³¹ See eg: European Commission Pharmaceutical Sector Inquiry Report 2008; European Commission Pharmaceutical Sector Inquiry Report 2009.

³² See the discussion on the Bolar provision in Section IV.A. for elaboration.

³³ EC Pharmaceutical Sector Final Report, 8 July 2009. At page 23 of the Executive Summary, the E.C. states that "The Commission will continue to strictly enforce the applicable Community law and, for instance, act against patent linkage, as according to Community legislation, marketing authorisation bodies cannot take the patent status of the originator medicine into account when deciding on marketing authorisations of generic medicines." In the 2008 Preliminary Report, the E.C. stated (at p. 14) more specifically that patent-linkage is considered unlawful under Regulation (EC) No 726/2004 and Directive (EC) No 2001/83. At p. 113, further elaboration is provided to the effect that: "Patent linkage refers to the practice of linking the granting of MA, the pricing and reimbursement status or any regulatory approval for a generic medicinal product, to the status of a patent (application) for the originator reference product. Under EU law, it is not allowed to link marketing authorisation to the patent status of the originator reference product. Article 81 of the Regulation and Article 126 of the Directive provide that authorisation to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in the Regulation and the Directive. Since the status of a patent (application) is not included in the grounds set out in the Regulation and in the Directive, it cannot be used as an argument for refusing, suspending or revoking MA."

³⁴ EC Pharmaceutical Sector Preliminary Report, at 22-23 (para 9). At para 895, the report states "- including intervention before regulatory bodies. Interventions before regulatory bodies (marketing authorisation authorities and pricing and

An evolving landscape such as this raises the question of whether the pharmaceutical industry is using linkage as an emerging stepping-stone in its efforts to reach across global borders to establish a uniform intellectual property regime in a distinctly non-uniform world. Moreover, a growing number of legal disputes have been reported whereby countries without linkage have attempted to import or export drugs where shipments are seized by other nations alleging that these shipments are in violation of domestic patent laws linked to international trade instruments such as TRIPS or other FTAs. Therefore, linkage regulations in respect of therapeutic products have quietly emerged as a powerful driver of drug regulation, access to essential medication, and public health costs on the global stage.

III. METHODOLOGY & RESEARCH QUESTIONS

When the group began its work, the obvious question to ask was - what should the focus be of future research on pharmaceutical linkage as it evolves globally from its North American roots? We noted that the study of structure-function relationships in living systems, both at the micro and macro levels, has served science especially well over the last century. The term “structure-function” refers to the relationship between the structural and functional elements of a system. As demonstrated by pioneering work in general systems theory and systems biology over the last half century, the interaction between structural and functional elements in a given system is bi-directional; that is, not only does structure influence function, but function also influences structure. As discussed further below, this occurs through various feedback mechanisms. The structure-function framework is particularly useful for the study of law, as specific statutory and regulatory language is intended, via relevant law and policy, to yield discrete and empirically observable outcomes.

The rapid spread of pharmaceutical linkage worldwide offers a unique and time sensitive opportunity to carry out empirical work on the system as it evolves globally from its original locus in North America. A major goal of our work on global pharmaceutical linkage will be to investigate the structural and functional aspects of different systems of linkage regulations, and their relationship on the one hand to drug availability costs, and expenditures, and incentives for innovation and protection of intellectual property rights on the other.

As in other complex political and economic systems,³⁵ the pharmaceutical linkage system is assumed to have structural and functional characteristics that can be identified and measured, and which in turn can serve as appropriate benchmarks to assess the performance of the system relative to its goals and objectives. Key decision makers, brand and generic pharmaceutical firms, the courts, patent counsel, consumers, payers, and other actors are assumed to interact in complex domestic and global networks through reasonably well-

reimbursement bodies) appear to be a standard tool in originator companies’ toolbox. Although contacting the health authorities may address legitimate concerns, it can also be used to delay or block the marketing authorisation or the pricing or reimbursement status of the generic product. In particular, by suggesting that the generic product is less efficient or safe or is not equivalent, raising patent infringement issues concerning the generic product in question and alleging that any decision favourable to the generic company would make the authorities liable to patent infringement damages (patent linkage), originator companies gain time and can create delays in granting marketing approval for the generic product and its entry into the market.

³⁵ Neil E. Harrison, ed. *Complexity in World Politics: Concepts and Methods of a New Paradigm* (Albany: State University of New York Press, 1997); Robert Jervis, *System Effects: Complexity in Political and Social Life* (Princeton: Princeton University Press, 1997); Barry Bozeman & Daniel Sarewitz, “Public Values and Public Failure in US Science Policy” (2005) 32 *Science and Public Policy* 119; Barry Bozeman, “Public Value Failure: When Efficient Markets May Not Do” (2002) 62 *Public Administration Review* 145; John D. Sterman, “All Models Are Wrong: Reflections on Becoming a Systems Scientist” (2002) 18 *System Dynamics Review* 501.

defined channels of communication.³⁶ Complex systems are characterized by broad rules that have increasing applicability and universality as the symmetry and elegance of the rules increase.³⁷ Indeed, previous work has demonstrated that this principle applies to innovation ecologies regulated by law,³⁸ particularly those where large-scale public and private rights revolving around technology must be balanced.³⁹

We use the term “structural” to refer to the broad administrative, legal and policy attributes of the linkage regime in differing jurisdictions. Together, these attributes form the initial starting conditions for operation of linkage regimes. The initial starting conditions, as in dynamical physical systems,⁴⁰ represent the sum of the political, economic and public policy conditions that together form the “take-off” point for a new law and the conditions in which it begins to operate. The structural aspect also encompasses the specific legal mechanisms that drive operation of linkage regimes in various jurisdictions. Identifying the structural attributes and mechanisms of individual linkage systems is important, as combined they provide the benchmark from which to assess the successes and failures of local systems in operation and their potential to combine to form a global an integrated regulatory regime.

Our preliminary research has identified a number of important structural aspects of pharmaceutical linkage, including: assessment in each jurisdiction of the original policy intent underpinning the linkage regime; the manner in which public health policy and economic policy is perceived by governments and the courts to converge or diverge through the linkage vector; the legal checks and balances found within the linkage regime designed specifically to maintain balance between the interests of brand and generic firms; the provisions in addition to linkage that were included in enabling legislation; and the growing expansion of the linkage concept beyond the drug approval-drug patenting nexus to encompass that between patenting and international trade mechanisms as well as how pharmaceutical linkage is in the process of informing the construction of new laws pertaining to follow-on biologics.

We use the term “functional” to refer to the outputs of the regulations in each jurisdiction as well as how these outputs functionally interact across borders to operate as a coherent global regulatory regime. The functional aspects reflect the behavior of the system as it evolves

³⁶ Peter Drahos, “Intellectual Property and Pharmaceutical Markets: A nodal governance approach” (2004) 77(2) *Temp. L. Rev.* 401-424.

³⁷ See generally Murray Gell-Mann, *The Quark and the Jaguar: Adventures in the Simple and the Complex* (New York: W.H. Freeman and Company, 1994). The practical implications of elegance and symmetry in physics and mathematics are explored elegantly by Gell-Mann in the videocast. “Beauty and Truth in Physics” *TED TV VideoCast (March 2007)*, online: *TED Blog* <http://blog.ted.com/2007/12/murray_gellmann.php>.

³⁸ William Wulf, “Changes in Innovation Ecology” (2007) 316 *Science* 1253; David H. Guston, “Innovation Policy: Not Just Jumbo Shrimp” (2008) 454 *Nature* 940; Fred Gault & Sasanne Huttner, “A Cat’s Cradle for Policy” (2008) 455 *Nature* 462.

³⁹ JB Ruhl, “Regulation by adaptive management: Is it possible?” (2005) 7(1) *Minnesota Journal of Law, Science and Technology* 21; Drahos 2004; Bouchard 2009.

⁴⁰ Albert-László Barabási, *Linked: How Everything is Connected to Everything Else and What It Means for Business, Science, and Everyday Life* (Plume, 2003); James Gleick, *Chaos: Making a New Science* (New York: Penguin, 1988); John H. Holland, *Adaptation in Natural and Artificial Systems* (MIT Press, 1992); John H. Holland, *Hidden Order: How Adaptation Builds Complexity* (Basic, 1995); Steven Johnson, *Emergence: The Connected Lives of Ants, Brains, Cities, and Software* (Scribner, 2002); Stuart Kauffman, *At Home in the Universe: The Search for the Laws of Self-Organization and Complexity* (Oxford University Press, 1995); Gregoire Nicolis & Ilya Prigogine, *Exploring Complexity: An Introduction* (New York: W.H. Freeman and Company, 1990); M. Mitchell Waldrop, *Complexity: The Emerging Science at the Edge of Order and Chaos* (New York: Simon & Schuster, 1992); Brian W. Arthur, “Positive Feedbacks in the Economy” (1990) 262 *Scientific American* 92, 92–99.

with time away from the initial starting conditions,⁴¹ in this case the U.S. Hatch Waxman regime. The functional aspects we have identified to study include: the impact of linkage regulations on the development of new and innovative drugs; the manner in which this is balanced by the timely entry of generic drugs; the degree to which market exclusivity is or can be extended solely by operation of the linkage regime; how brand firms use the linkage system in order to extend market exclusivity on high value drugs; the costs to consumers or other payers of extended exclusivity; the costs of extended exclusivity based on patents that are ultimately found to be invalid or not infringed; the impact of differing mechanisms of regulatory oversight on drug pricing and reimbursement; and the role of empirical studies for the legitimacy of linkage regulations.

Complex legal, scientific, medical, and economic issues such as those encompassed by the linkage regime lend themselves well to study by a network, or consortium, of scholars and practicing lawyers.⁴² A unique advantage of a network-based approach is that studying linkage in different jurisdictions allows for both: (1) an investigation of the structural and functional characteristics of local linkage regimes with different initial starting conditions and different legal mechanisms of operation; and (2) the identification of general rules of linkage as the different national forms of linkage interact and influence global pharmaceutical regulation. The former provides a *descriptive* mechanism for assessing the successes and failures of different regimes while the latter provides a *prescriptive* approach for key decision makers to revise, institute or abolish linkage regulations according to the goals and objectives of differing nations.

The objective of our research, beginning with this Article, is to produce and utilize empirical knowledge relating to different linkage regimes as a knowledge translation tool for assessing the strengths, weaknesses, successes and failures of pharmaceutical linkage in individual nations and how they combine to form a global system of pharmaceutical linkage. Different economic, public health and political systems present a different set of initial starting conditions not only for the *de novo* operation of linkage regulations in each jurisdiction as they come into force, but also for how these systems evolve, grow, and adapt to changing conditions over time. Indeed, our early data suggests substantial differences between jurisdictions in this regard, and that these differences may be fundamentally responsible for the opposition of certain nations and economic regions to pharmaceutical linkage and the varying degrees of success of those employing them in the twin policy goals of encouraging the development of new and innovative drugs while also facilitating the timely entry of generic drugs and access to essential medications. Examples of a number of such differences follow.

⁴¹ Harrison 1997; Jervis 1997. See also: Clifford Shearing & Jennifer Wood, “Nodal Governance, Democracy, and the New ‘Denizens’”, (2003) 30 J.L. & Soc’y 400, 401-06; Les Johnston & Clifford Shearing, *Governing Security: Explorations In Policing And Justice* ch. 8 (2003); Scott Burris, “Governance, Microgovernance, and Health” (2004) 77 Temp. L. Rev. 335, 357.

⁴² The authors represent nations with mature linkage regulations (U.S.; Canada), relatively young regulations (Australia; China, Mexico), those without regulations but with certain practices that may operate to parallel linkage (E.U.) and those where both the existence and scope of linkage regulations are the subject of intense public scrutiny and litigation (India; South Korea). The verb “proposed” is used in the title of this Article with intent, as future work by the group will be shaped by the availability of grant funding to support a large-scale global collaboration of this nature.

IV. STRUCTURAL & FUNCTIONAL ASPECTS OF PHARMACEUTICAL LINKAGE

A. *Original Policy Intent*

An excellent starting point for a global analysis of pharmaceutical linkage is the “original policy intent” underpinning linkage in differing jurisdictions. Original policy intent presents a critical issue for determination of whether or not legislation is *intra vires* or *ultra vires*, as governments have specific legal and policy goals in mind when drafting law and regulations that are reviewable by the courts in judicial review proceedings.⁴³

A number of questions arise relevant to original policy intent as it pertains to different forms of linkage. In practice these can, and typically do, vary substantially from one nation to the next. This is not surprising given the differing political, economic and technological landscapes involved. A related issue is when the policy grounds put forward are similar in varying jurisdictions, but the legal mechanisms underpinning operation of the linkage regime differ, with potentially varying outputs. How do the grounds offered in support of linkage relate to other mechanisms for intellectual property protection for pharmaceuticals, such as data protection, patent term extension, etc.? Have the mechanisms favoring legal protection of pharmaceutical products been balanced by other mechanisms in favor of price control? Our preliminary analysis indicates significant differences among jurisdictions, with some favoring strong intellectual property protection and linkage regulations with and without price controls, those which are considering controls, and those with express forms of anti-evergreening provisions balanced with regulation of generic drug prices.

For example, in the United States where the linkage regime first came into force, the purpose of Hatch Waxman was explicitly to balance two competing policy objectives: to induce brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while enabling competitors to bring cheaper, generic copies of those drugs to market as soon as possible.⁴⁴ Indeed, during trade negotiations leading up to linkage in the United States, Canada and Australia,⁴⁵ claims were made to the effect that linkage regulations were necessary to provide incentives to firms to engage in high risk research and development. In each instance, universities were particularly keen to hitch their wagon to the regulations.⁴⁶ Senator Hatch, at the time the American legislation came into force said “The public receives the best of both worlds – cheaper drugs today and better drugs tomorrow”.⁴⁷ The same is true in Canada, as outlined clearly in the government’s Regulatory Impact Analysis Statements on topic.⁴⁸ Therefore, in addition to stimulating pioneering drug

⁴³ Cameron Hutchinson. *Which Kraft Statutory Interpretation? A Supreme Court of Canada Trilogy on Intellectual Property Law*. 46 A.L.R. 1 (2009).

⁴⁴ *Abbott Labs. v. Young*, 920 F.2d 984, 991 (D.C. Cir. 1990); H.R. Rep. No. 98-857, pt. 1, at 14–15; *Mylan Pharmaceutical v. Bristol-Myers Squibb*. 268 F.3 1323, at 1326.

⁴⁵ Tancer 1997; Harrison 2001; Bouchard 2011; Thomas A Faunce & Joel Lexchin: “Linkage’ pharmaceutical evergreening in Canada and Australia” (2007) 4 *Australia and New Zealand Health Policy* 8.

⁴⁶ Bouchard 2011. See also: Tancer 1997; Harrison 2001.

⁴⁷ Congressional Record – Senate at 23764 (August 10, 1984), as cited in Epstein and Kuhlik 2004, at note 24.

⁴⁸ Evidence of legislative intent regarding balancing patent enforcement and generic entry can be found in early RIAS documents. See generally: *Canada Gazette*. Vol. 132, No. 7. 12 March 1998; *Id.* Vol. 133. No. 21. 1 October 1999. Evidence of legislative intent regarding the “original policy intent” of encouraging development of new and innovative drugs can be found in both RIAS and related Guidance Documents: *Canada Gazette*. Vol. 138. No. 50. 11 December 2004; *Id.* Vol. 140. No. 24. June 17, 2006; *Id.* Vol. 142. No. 13. 25 June 2008; Health Canada Guidance Document. *Patented Medicines (Notice of Compliance) Regulations*. 3 April 2009. An articulation of the government’s pharmaceutical policy as it relates to the NOC Regulations can be found in the 2006 RIAS, which (at 1510) states: “The Government’s

development, a second major policy goal of linkage in both originating jurisdictions was to facilitate timely generic entry.⁴⁹

However, while the policy goals may be similar, the factual baseline for legislation may differ significantly in different nations, with the result that outcomes may change accordingly. The U.S. and Canada present an excellent case study in this regard. Prior to linkage in the United States, a large number of drugs were off patent yet not marketed by generics due in large part to regulatory costs resulting from the inability to rely on the data in the original approval.⁵⁰ This mechanism was eventually provided by Hatch Waxman, with the result that, notwithstanding a certain level of gaming of the system,⁵¹ the United States developed a strong generic industry that is paralleled by a strong brand pharmaceutical industry. In contrast, Canada had a substantial domestic generic industry prior to linkage predicated in part by provisions allowing for compulsory licensing of pharmaceuticals.⁵² The result of linkage in Canada, as some have claimed, is the diminution of the generic industry,⁵³ rising generic drug prices,⁵⁴ and no change in the level of global competitiveness for national life sciences firms.⁵⁵ A similar situation has developed in India, which is in the midst of an intense legal battle over whether to institute some form of pharmaceutical linkage.⁵⁶ In contrast, the law relating to linkage in Mexico has just been interpreted to include not only active ingredient patents but also patents covering pharmaceutical formulations.⁵⁷ Processes

pharmaceutical patent policy seeks to balance effective patent enforcement over new and innovative drugs with the timely market entry of their lower priced generic competitors. The current manner in which that balance is realized was established in 1993, with the enactment of Bill C-91, the Patent Act Amendment Act, 1992, S.C. 1993, c. 2.”

⁴⁹ Daniel R. Cahoy, “Patent Fences and Constitutional Fence Posts: Property Barriers to Pharmaceutical Importation” (2005) 15 *Fordham Intell. Prop. Media & Ent. L.J.* 623.

⁵⁰ For example, in the U.S. generics could not use NDA holder’s data to demonstrate safety and efficacy and were forced to conduct clinical trials to support market authorization. (Avery 2008, at 175, citing Soehnge, note 23: Holly Soehnge, “The Drug Price Competition and Patent Term Restoration Act of 1984: Fine-Tuning the Balance Between the Interests of Pioneer and Generic Drug Manufacturers” (2003) 58 *Food & Drug L.J.* 51, 52.) Before Hatch Waxman, the U.S. Food and Drug Administration demonstrated that approximately 150 brand drugs were on market with expired patents but with no generic equivalents, resulting in hundreds of million dollars in out of pocket consumer expenditures. (H.R. Rep. No. 98-857, pt. 1, at 17 (1984)).

⁵¹ Caffrey 2003; Bulow 2003; Avery 2008; Aidan Hollis, “Closing the FDA’s Orange Book,” (2001) 24(4) *Regulation* 14-17

⁵² Tancer 1997; Harrison 2001.

⁵³ Ed Hore, *Patently Absurd: Evergreening of Pharmaceutical 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>; Lexchin J., “After compulsory licensing: Coming issues in Canadian pharmaceutical policy and politics” (1997) 40(1) *Health Policy* 69-80 Joel Lexchin, *Intellectual Property Rights and the Canadian Pharmaceutical Marketplace: Where do We Go from Here?*, 35 *Int’l. J. Health Serv.* 237, 243 (2005).

⁵⁴ Brett Skinner, “Generic Drugopoly: Why non-patented prescription drugs cost more in Canada than in the United States and Europe” (2004) 82 *Public Policy Sources*. Fraser Institute. 1-36.

⁵⁵ *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).

⁵⁶ In 2008, Bayer moved the High Court at Delhi to seek a declaration against the drug regulatory authority, Drug Controller General of India (DCGI) directing the DCGI to refrain from passing an order of market approval for an Indian generic company, Cipla for its generic version of the drug ‘Soraniib’. Bayer based its arguments on the assertion that Section 2 of the Drugs and Cosmetics Act read with section 48 of the Patents Act provided for the concept of patent linkage. Justice Ravindra Bhatt of the Delhi High Court dismissed Bayer’s arguments for creating linkage between patent grants and marketing approvals. Bayer appealed the decision of the Single Judge before a Division Bench of the Delhi High Court. The Division Bench dismissed the appeal. Bayer filed an appeal from decision of the Division Bench of the Delhi High Court to the Supreme Court of India. On December 1st 2010, the Supreme Court dismissed Bayer’s appeal refusing to interfere with the finding of the High Court of Delhi (*Bayer Corp. & ANR. v. Union of India & ORS. Supreme Court of India. DC 6540/2010*).

⁵⁷ Juan Luis Serrano. *Mexican Supreme Court Decides on Broad Interpretation of Linkage Regulations* (9 March 2010), online: Patent Docs Blog < <http://www.patentdocs.org/2010/03/mexican-supreme-court-decides-on-broad-interpretation-of-linkage-regulations.html>>.

are still expressly excluded in Mexico; the inclusion of patents covering uses remains a hotly contested issue.

In addition to jurisdictional variability in the establishment of the generic drug industry prior to linkage, another important contextual issue we have identified is the use of the Bolar, or “safe harbor,” provision as a policy lever in pharmaceutical linkage regimes. The impetus for a focus on the Bolar provision is that the legal nexus between drug approval and drug patenting under linkage can trace its history back to insertion of early working provisions into the infringement section of patent legislation in the United States and Canada. For this reason, the law and policy relating to the Bolar provision is pivotal to the analysis of the effectiveness and efficiency of pharmaceutical linkage as a policy vehicle.

Despite the “scant legislative history” of legislation underpinning the linkage regime,⁵⁸ the United States Committee on Energy and Commerce noted in its influential report that the locus of the legal nexus between drug approval and drug patenting under Hatch Waxman was specifically through the infringement section of patent legislation. In this manner, approval and marketing of generic substitutes was fundamentally linked to patents associated with new and innovative drugs developed by brand pharmaceutical firms. As to which patents were considered relevant to the generic substitute, the Committee on Energy and Commerce stated the law would be aimed at protecting the first product patent per drug or, if there was no product patent, the first process patent. In addition, the Committee recognized that “in some instances” (e.g., situations where there were product and use patents relevant to an existing marketed product as opposed to only a product patent) the listing of multiple patents on the patent register would be foreseeable.⁵⁹

The balance of the early-working exemption favoring generics gauged against the ability of brand firms to commence legal action prior to generic marketing was viewed by the Committee on Energy and Commerce to “fairly balance” the rights of brand patent owners with those of generic entrants that wish to contest the validity and/or infringement of a patent before such patents expire.⁶⁰ No further protection for brand firms was deemed needed in view of other incentives to firms for innovative drug development.

While allowing for multiple patents to be listed on the register, the Committee on Energy and Commerce nevertheless explicitly noted that the ability of brand firms to delay generic entry using the Hatch Waxman amendments should be narrow both in scope and time; the proper time for generic entry being “the expiration date of the valid patent covering the original product” and that “there should be no other direct or indirect method of extending

⁵⁸ *Mylar Pharmaceuticals v. Bristol-Myers Squibb Co.* 268 F.3d 1323d, at 1332.

⁵⁹ House Report No. 98-857(I) [H.R.(I)] (at 8): Acknowledging that multiple patents would be listed on the patent register to delay generic entry. Specifically, the Committee recognized two different types of patent being properly listed on the patent register. These included: *all* product patents which claim the listed drug and *all* use patents which claim an indication For the drug for which the applicant is seeking approval (hereafter described As a controlling use patent), the applicant must certify, in his opinion And to the best of his knowledge, as to one of four circumstances [Emphasis added]. Later in the text the Committee recognized that “in some instances an applicant will have to make multiple certifications with respect to product or controlling use patents. For example, if the product patent has expired and a valid controlling use Patent will not expire for three years, then the applicant must certify that one Patent has expired and the other will expire in three years. The committee intends that the applicant make the appropriate certification for each product and controlling use patent.”

⁶⁰ *Id.* At 13, the Committee noted “this additional remedy permits the commencement of a legal action for patent Infringement before the generic drug maker has begun marketing. The committee believes this procedure fairly balances the rights of a patent owner to Prevent others from making, using, or selling its patented product and the Rights of third parties to contest the validity of a patent or to market a product which they believe is not claimed by the patent.

patent term.”⁶¹ The extension of patent protection was viewed to be effectively and directly accomplished by the Title II Hatch Waxman amendments allowing for patent term restoration. The standard for listing is that a claim of patent infringement “could reasonably be asserted.”⁶² The legal nexus between drug approval and drug patenting under the Canadian linkage regime is also through the infringement section of relevant patent legislation.⁶³ Thus, in order to assess the effectiveness of linkage as a policy lever one must do so through the lens of the Bolar provision as it works in tandem with infringement law and other legislation intended to encourage the development of new and innovative drugs while also facilitating the timely entry of generic drugs. For these reasons linkage legislation is said to “balance competing policy interests.”

As well described in the literature, the Bolar provision is enshrined in the safe harbor provision of Hatch Waxman (35 USC § 271(e)(1)) and allows “early working” of patented inventions ahead of generic entry. While the terms Bolar provision and early working provision are often used conterminously, recent jurisprudence suggests that one may be enfolded within the other and not vice versa. As noted by the United States Supreme Court in *Merck v. Integra*,⁶⁴ the purpose of the safe harbor provision is to protect basic research and development activities that contribute to the generation of information required by drug regulators to approve a new drug product. This can be compared to the Bolar provision, which is more narrowly aimed at facilitating timely generic entry after patent protection for a new product expires. In language reminiscent of that employed by the High Court of Delhi in *Bayer v. India* to reject linkage,⁶⁵ the request to be exempted from patent infringement proceedings to work-up the generic product ahead of patent expiry was denied in the original case of *Roche v. Bolar*.⁶⁶ However, shortly after *Bolar* was released, the United States Congress enacted an exception to the patent infringement rule in order to facilitate timely generic entry by reducing the regulatory lag for bioequivalence testing and regulatory approval.⁶⁷

⁶¹ At 30, the Committee stated: article 1, section 8, clause 8 of the constitution empowers congress to grant exclusive rights to an inventor for a limited time. That limited time should be a definite time and, thereafter, immediate competition should be encouraged. For That reason, Title I of the bill permits the filing of abbreviated new drug applications before a patent expires and contemplates that the effective approval Date will be the expiration date of the valid patent covering the original Product. Other sections of title ii permit the extension of the term of a patent for a definite time provided certain conditions are met. There should be no other direct or indirect method of extending patent term.

⁶² *Id.*, 30.

⁶³ *Biolysse Pharma Corp. v. Bristol-Myers Squibb Co.* 2005 SCC 26; *AstraZeneca Canada Inc. v Canada (Minister of Health)*, 2006 SCC 49, at para 38.

⁶⁴ *Merck KGaA v. Integra Lifesciences I, Ltd., et al.*, 545 U.S. 193 (2005), citing District Court (F.3d, at 863), at 200.

⁶⁵ At para 7, Justice Nichols states: “ Bolar argues that even if no established doctrine exists with which it can escape liability for patent infringement, public policy requires that we create a new exception to the use prohibition. Parties and amici seem to think, in particular, that we must resolve a conflict between the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301-392 (1982), and the Patent Act of 1952, or at least the Acts' respective policies and purposes. We decline the opportunity here, however, to engage in legislative activity proper only for the Congress.” This language can be compared to that of the High Court of Delhi discussed supra note 90.

⁶⁶ *Roche Products Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 04/23/1984).

⁶⁷ In *Merck* supra, Justice Scalia stated (at 195): It is generally an act of patent infringement to “mak[e], us[e], offe[r] to sell, or sell[] any patented invention ... during the term of the patent therefor.” § 271(a). Drug Price Competition and Patent Term Restoration Act of 1984, §202, 98 Stat. 1585, as amended, 35 U.S.C. §271(e)(1), which provides: “It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) ...) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs”

It is reasonable to speculate that the policy grounds, expected outputs, and legal mechanisms underpinning brand and generic drug development pathways do, and indeed should, differ. Indeed, as a policy vehicle the safe harbor provision seems to go beyond the scope of *Bolar* to facilitate generic entry. For example, in the U.S Supreme Court's *Merck* decision, Justice Scalia held that §271(e)(1) protected all basic research leading up to and “reasonably related” to the process of developing information for a regulatory submission.⁶⁸ Justice Scalia specifically noted that the safe harbor provision was *not* limited in scope to be so narrow as to *only* support an ANDA, or generic submission.⁶⁹

Reading *Merck* together with *Bolar* and the Hatch Waxman amendments, it seems safe to say that while the safe harbor provision of §271(e)(1) facilitates generic entry, the scope of the provision as an exception to patent infringement is broader and more inclusive; it encourages research and development into both new and generic drugs. On the one hand, the safe harbor provision protects innovative research activities from infringement litigation by patent owners in circumstances where such research can reasonably lead to a regulatory submission. In the absence of such “safe harbor”, research of this nature would be chilled to the detriment of both competition and the public.⁷⁰ On the other hand, the safe harbor provision protects generic firms from infringement while working up their regulatory submissions. However, it does not necessarily follow that if a certain scope of patents is subject to the safe harbor provision to encourage competition and innovation, that an equally broad scope of patents must be included under the pharmaceutical linkage umbrella in order to delay generic entry on older drugs.

While *Bolar* has been maintained as legal justification for linkage in the United States,⁷¹ Canada,⁷² and elsewhere,⁷³ it is somewhat of a surprise that the policy grounds have never been elucidated as to how or indeed why infringement law may be properly used to extend beyond early working of *a* patent on *a* particular drug to linkage with *many* patents on *many*

⁶⁸ At 206 (para 11), the court held “The statutory text does not require such a result. Congress did not limit § 271(e)(1)'s safe harbor to the development of information for inclusion in a submission to the FDA; nor did it create an exemption applicable only to the research relevant to filing an ANDA for approval of a generic drug. Rather, it exempted from infringement *all* uses of patented compounds “reasonably related” to the process of developing information for submission under *any* federal law regulating the manufacture, use, or distribution of drugs. See *Eli Lilly*, 496 U.S., at 674, 110 S.Ct. 2683. We decline to read the “reasonable relation” requirement so narrowly as to render § 271(e)(1)'s stated protection of activities leading to FDA approval for all drugs illusory. Properly construed, § 271(e)(1) leaves adequate space for experimentation and failure on the road to regulatory approval: At least where a drug maker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is “reasonably related” to the “development and submission of information under ... Federal law.” § 271(e)(1).

⁶⁹ At 206: “In the vast majority of cases, neither the drug maker nor its scientists have any way of knowing whether an initially promising candidate will prove successful over a battery of experiments. That is the reason they conduct the experiments. Thus, to construe § 271(e)(1), as the Court of Appeals did, not to protect research conducted on patented compounds for which an IND is not ultimately filed is effectively to limit assurance of exemption to the activities necessary to seek approval of a generic drug: One can know at the outset that a particular compound will be the subject of an eventual application to the FDA only if the active ingredient in the drug being tested is identical to that in a drug that has already been approved.

⁷⁰ *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.); *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). 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).

⁷¹ *Mylan Pharmaceuticals v. Bristol-Myers Squibb Co.* 268 F.3d 1323, at 1326; *Merck KGaA v. Integra Lifesciences I, Ltd., et al.*, 545 U.S. 193 (2005).

⁷² Bouchard 2011.

⁷³ EC Pharmaceutical Inquiry Final Report 2009; *Bayer Corporation & Ors. v. Union of India & Ors.* LPA 443/2009.

drugs.⁷⁴ For example, the rationale used to support linkage in Canada was that generic entry would occur on expiry of the “main patent” on a given product.⁷⁵ The maximal delay for generic products was claimed to be equivalent to that for generic approval prior to linkage, or two to three years. No legal mechanism or policy grounds were offered to prohibit generic entry based on the on expiry of multiple patents that relate to the new and innovative drug only distantly in time, particularly the expiry of multiple patents on multiple related drug forms (tablet “following on” capsule form, monohydrate “following on” dihydrate crystalline form, besylate salt “following on” mesylate salt form, enantiomer “following” on racemic mixture, etc.). Provisions enabling the extension of market exclusivity in this manner only appeared once the regulations accompanying amendments to patent legislation were published.⁷⁶

The idea that only a “main patent” should be protected is congruent with the statement by the U.S. Committee on Energy and Commerce to the effect that the appropriate time for generic entry was the expiration date of the valid patent covering the original product and that there should be no further method of extending patent term. In light of the statement by the Federal Circuit in *Mylan*⁷⁷ that Hatch Waxman not only creates the statutory act of infringement but also defines the conditions under which a defense to infringement is available, the number and scope of patents listed on the patent register is crucial to assessing whether the legislation is working consistent with its objective of balancing the competing policy objectives of stimulating innovative research and enhancing generic entry. Thus, it is somewhat of a surprise that both the courts and government branches responsible for bringing into force the originating linkage regimes in North America have remained largely silent on the policy grounds underpinning the multiple patent listing model other than to say that it fairly balances the rights of brand patent owners with those of generic entrants under certain narrow conditions.⁷⁸

Given the lack of policy debate combined with the significant public health implications involved, it is not surprising that some appellate courts have taken a dim view of unduly broadening the drug approval-drug patenting nexus to the detriment of generic entry. In its leading decisions on linkage, *Biolyse*⁷⁹ and *AstraZeneca*,⁸⁰ the Supreme Court of Canada narrowly construed its analysis on the breadth of drug submissions and patent listing within the terms of the Patent Act.⁸¹ The court held that in cases under the NOC Regulations that it was necessary to undertake a “patent-specific analysis” rather than a broad inclusive reading of the terms drug submission and patent listing that would enable undue prolongation of market exclusivity. This was taken to be consistent with the of the *quid pro quo* traditional patent bargain.⁸²

⁷⁴ Bouchard 2011.

⁷⁵ *Id.*

⁷⁶ NOC Regulations, 1993.

⁷⁷ *Mylan Pharmaceuticals v. Bristol-Myers Squibb Co.* 268 F.3 1323, at 1331.

⁷⁸ *Id.* At 15, the Committee noted “this additional remedy permits the commencement of a legal action for patent infringement before the generic drug maker has begun marketing. The committee believes this procedure fairly balances the rights of a patent owner to Prevent others from making, using, or selling its patented product and the Rights of third parties to contest the validity of a patent or to market a product which they believe is not claimed by the patent.

⁷⁹ *Biolyse Pharma Corp. v. Bristol-Myers Squibb Co.* 2005 SCC 26, at 26.

⁸⁰ *AstraZeneca Canada Inc. v Canada (Minister of Health)*, 2006 SCC 49, at para 38.

⁸¹ *Patent Act*, R.S.C., 1985, c. P-4.

⁸² *AstraZeneca* 2006, at 16 and 39. A “patent-specific analysis” was recently confirmed by Health Canada in its 2009 Guidance Document relating to the NOC Regulations: HEALTH CANADA GUIDANCE, supra note 26, at page 26. In

In *Bayer v. India*, the High Court of Delhi went one step further, holding that the North American model of linkage, encompassing as it does multiple patents listed per drug or groupings of related drugs, would undermine the early-working aspect of Bolar, deny space for generic drugs in the marketplace, and mitigate the positive impact of generic drugs on health care expenditures and costs.⁸³ The court based its decision in part based on the finding that patent linkage is a “TRIPS-Plus” concept and that India had only signed on to TRIPS. Justice Muralindhar noted for the court that “Worldwide there is a raging debate on whether patent linkage should be permitted. There is no uniformity in the policy of different countries,”⁸⁴ recognizing earlier in the decision that there was growing opinion in developed countries, including the European Union, cautioning against linkage.⁸⁵

Based on a middle way reading of appellate cases such as these, one could conclude that the primary problem with pharmaceutical linkage may not be the concept of linkage itself, e.g., balancing generic early-working and brand patent protection, as much as the breadth of the legal nexus between drug approval and drug patenting as well as how the regulations operate within the larger system of policy levers intended to stimulate brand and generic drug development. Both issues are dealt with in detail in the discussion that follows.

[Fig. 1 Near Here]

Fig. 1 illustrates the complex system of legal incentives for the development of brand and generic drugs, using the United States as an example. This system includes a number of interrelated policy levers such as traditional patent incentives for firms and universities under patent and Bayh-Dole legislation, the broad research exemption for preclinical and clinical research for originator firms under Title I of Hatch Waxman, multiple data exclusivity periods for regulatory submissions by originator firms under TRIPS and FTAs such as NAFTA, extended patent terms to originator firms to compensate for regulatory delays under Title II of Hatch Waxman, extended patent protection for originators under the linkage regulations provisions of Title I of Hatch Waxman for products in later stages of development, and the safe harbor for generic products under Title I of Hatch Waxman. As indicated by a comparison of y axis data, while originator products have a greater level of innovation, entail a greater degree of research and development, and have a broader scope of safe harbor protection than do their generic counterparts, generic products nevertheless have a substantial public welfare benefit due to their fractional cost compared with pioneering products. Of note, notwithstanding the large public welfare benefit ascribed to generic drugs, only one of the seven policy levers described in Fig. 1 is aimed at facilitating generic entry; the Bolar provision.

addition to acknowledging that a “patent-specific analysis” is necessary when interpreting the NOC Regulations the government further stated (at 28) that only certain patents are “eligible” for protection under the NOC Regulations, indicating that not all patents fall within the purview of the regulations. See also: *Ferring v. Canada* 2007 FC 300, at paras 51-57.

⁸³ *Bayer v. India*, at para 7 and 12. Others, however, have taken the opposite approach in India, where generic firms have argued no cause of action for a *quia timet* action (apprehending the impending threat of generic entry) exists given that the Bolar provision allows a generic company to make, construct, use, sell or import a patent invention for the purpose of development and submission of information required for regulatory purposes. *F. Hoffmann La Roche v Matrix Laboratories Ltd*, C.S.No. 801 of 2010, High Court of Judicature at Madras (pending).

⁸⁴ *Id.*, at para 32.

⁸⁵ *Id.*, at para 7.

It seems reasonable to assume that legal vehicles such as those depicted in Fig. 1 are intended to work together to foster innovation while also providing as much public value as possible by facilitating generic entry.⁸⁶ Indeed, while upholding the constitutionality of the Hatch Waxman amendments, the Committee on the Judiciary stated in 1984 that the amendments were consistent with the traditional role of Congress to “balance the need to stimulate innovation against the goal of furthering the public interest”, in this case increasing the availability of generic substitutes.⁸⁷ However, while the rationale for linking the Bolar exemption to multiple patents listed on the patent register may at one time have been aimed at balance (e.g., a safe harbor abeyance from infringement during the working up phase to the detriment of patentees balanced by effective intellectual property protection on innovative drugs in favor of patentees), what empirical data exists at this point suggests the balance effected through this specific legal mechanism may not working as envisioned.

One of the most fertile areas of debate regarding pharmaceutical linkage is whether the provision allowing multiple patents to be listed on the patent register is the main culprit when the system does veer off to one side as opposed to strategic abuse of the automatic stay provision, which is usually singled out as the water thrown on the fire of timely generic entry.⁸⁸ Ironically, in *Bolar*, litigation was focused on a single patent (relating to the sleep aid flurazepam), rather than a cluster of product, use, route of administration, process and combination therapy patents that in turn can be listed on multiple chemical forms of the same original drug.⁸⁹ The conclusion one can draw from this analysis is that the drug approval-drug patent nexus under linkage law should be construed narrowly rather than broadly, consistent with its original purpose in *Bolar*.

For example, just because infringement of one or more patents may be held in abeyance while a generic works-up its manufacturing processes in service of regulatory approval does not justify the grant of prolonged market exclusivity for a cache of older drugs protected by a large group of patents, many of which may be invalid or not infringed by the generic equivalent.⁹⁰ Moreover, the policy goal of holding patent infringement in abeyance under the safe harbor provision is the desire that patents equally strong to those held in abeyance will be associated with the regulatory submission of the party requesting abeyance and that competing products will be developed. It is reasonable to assume there should be an analogous reciprocity under the linkage regime, as generic products are by nature less innovative but nevertheless have substantial social benefits owing to price competition. In light of the foregoing, it seems reasonable to conclude that generic products should not be prevented from gaining regulatory approval by a cluster of follow-on patents that are associated with new and innovative drug products only distantly in time; the original goal of *Bolar* was to minimize the regulatory lag for generic firms to work-up regulatory submissions and obtain approval. This can be contrasted to the much more substantial increase in cumulative patent protection that can result from listing multiple weak patents against one or more marketed drugs.

The discussion thus far suggests that it is plausible that provisions in linkage laws allowing multiple patents to be listed against a given drug over time with little or no requirement for

⁸⁶ H.R. 98-857(II), at 25.

⁸⁷ H.R. 98-857(II), at 26.

⁸⁸ Caffrey 2003; Bulow 2003; Avery 2008; Hore 2004.

⁸⁹ Bouchard 2009.

⁹⁰ FTC Study 2002; Hore 2004.

proportional public welfare benefit represents the weak link in the regulations as they currently operate. This can be argued for two reasons. First, because patents may be listed on the patent register so long as they meet statutory listing requirements and are deemed “relevant” to the marketed drug, a term that has proved to be very difficult to assess legally.⁹¹ The case law indicates the relevance requirement is very minimal,⁹² with the effect that often dozens of patents are listed per drug, particularly for high value pharmaceuticals.⁹³ The rationale typically used for this low listing requirement has been that drug regulators are not equipped to assess patents on the register. Ironically, In *Bayer v. India*, the same rationale was used to reject linkage.

Second, and more importantly, is the fact that multiple patents do not exist in isolation; both in scope and time. They are interconnected to multiple related drugs through weak regulatory submission requirements,⁹⁴ which in turn allow for large numbers of follow-on drugs comprising a temporally evolving cluster of related products and patents.⁹⁵ As a result, originator firms appear to have transferred the thrust of their competitive activities away from competition between each other and towards encouraging competition within their own formulary departments. The goal of this internal competition appears to be to produce as many follow-on drugs as possible in order to keep generics off market for as long as possible. This has been referred to as portfolio-based innovation, analogous to portfolio financing.⁹⁶ There is no question that portfolio-based innovation is a superb form of innovation from an organizational perspective. The question is, is this form of innovation desirable from a social welfare perspective?

In the pre-linkage era, pharmaceutical firms typically developed discrete drugs that were associated with one or a small number of patents.⁹⁷ Once that small number of patents expired, products could be copied. In this, pharmaceutical firms were in a similar position to firms in other industries, including those in other technology-heavy sectors.⁹⁸ An argument can be made that this process in turn provided an incentive for competition between brand

⁹¹ *Mylan Pharmaceuticals v. Bristol-Myers Squibb Co.* 268 F.3d 1323; *AstraZeneca v. Apotex, Minister of Health* 2004 FC 1277.

⁹² Guidance Document: Patented Medicines (Notice of Compliance) Regulations, http://www.hc-sc.gc.ca/dhp-mpps/prodpharma/applic-demande/guide-ld/patmedbrev/pmreg3_mbreg3-eng.php (Apr. 3, 2008). See also: *AstraZeneca Canada Inc. v. Canada*, [2006] 2 S.C.R. 560, 2006 SCC 49 (Can.); *Wyeth Canada v. Ratiopharm, Inc.*, [2008] 1 FC 447.

⁹³ Bouchard 2009; 2010; Hemphill and Sampat 2011; Hemphill and Lemley 2011.

⁹⁴ Bouchard 2010.

⁹⁵ Bengt Domeij, *Pharmaceutical Patents in Europe*. (Kluwer Law International, 2000); Bengt Domeij, “Initial and Follow-on Pharmaceutical Inventions in Europe” in Ove Granstrand, ed. *The Economics and Law of Intellectual Property* (Kluwer Law International, 2003) 177-198. See also: Sawicka & Bouchard 2008; Bouchard 2009; Bouchard 2010.

⁹⁶ William Kingston. “Intellectual Property’s Problems: How Far is the U.S. Constitution to Blame?” (2002) 4 Intellectual Property Quarterly 315.

⁹⁷ The European Commission, in its Pharmaceutical Sector Enquiry Final Report, states (at para (383) that many pharmaceutical firms experienced a change in their drug development strategies about the time Hatch Waxman came into force. Quoting leadership at one originator company, the Commission noted that: “Before end 80s: Products mainly NCEs which were protected by the one patent- [...] Late 80s – early 90s[...] Expansion of the portfolio to cover lifecycle initiatives, to extend protection time for product and the brea[d?]th of the protection trying to keep competition further away.” At para 388, the Commission further noted that “Originator companies could thus use their web of patents to prevent or delay generic entry, as illustrated by the following originator company’s quote: “We were recently successful in asserting the crystalline form patent in [name of country], where we obtained an injunction against several generic companies based on these patents by ‘trapping’ the generics: they either infringe our crystalline form patent, or they infringe our amorphous form process patent when they convert the crystalline form to the amorphous form. [...] The availability of ‘trapping’ strategy will be evaluated on an on-going basis.”

⁹⁸ Dan Burk & Mark A. Lemley. “Is Patent Law Technology Specific?” (2002) 17 Berkeley Technology Law Journal. 1157-1208.

firms, consistent with judicial articulations of the ends and means underpinning the traditional patent bargain.⁹⁹

A different situation has evolved in the post-linkage era, where loopholes in linkage laws may conduce to a drug development strategy that favors the development of product clusters.¹⁰⁰ Product clusters are hypothesized to be comprised of an expanding number of follow-on drugs evolving from a single new and original drug, surrounded by a constellation of patents which interconnect products within a given cluster through a combination of traditional infringement law and the listing provision under emerging linkage law. These patents serve two different yet vital functions. First, they provide support for follow-on drug candidates via traditional infringement law, and second they provide fodder for listing on patent registers to delay generic entry under linkage law. Perhaps most important for policy-makers, it may be the sum of the interactions between multiple drugs and multiple patents in these clusters that most effectively chills generic entry.

Given that empirical data are only beginning to be reported on pharmaceutical linkage, this clustering effect may present a more substantial barrier to generic entry than previously recognized, and it is not clear whether generics are being adequately compensated for taking on the risk of litigation.¹⁰¹ Our work thus far suggests this conclusion may apply more strongly in jurisdictions where litigation under linkage regulations does not constitute final decision, where linkage laws do not provide generic entrants with an exclusivity period for first movers compared to those that do not, where the relevance requirement for patent listing is comparatively weak, where patents are comparatively easier to obtain, and where the evidentiary standard for the approval of new and follow-on drugs is comparatively low.

Evidence suggesting that the Bolar provision was narrowly intended to encourage generic entry and that this narrow exception to patent law was ultimately in service of a short-term exemption that favors, not restricts, competition can be found in the words of the Committee on Energy and Commerce to whom the Hatch Waxman bill was referred:

The purpose of sections 271(e)(1) and (2) is to establish that experimentation with a patented drug product, when the purpose is to prepare for commercial activity which will begin after a valid patent expires, is not a patent infringement.

Article 1, section 8, clause 8 of the Constitution empowers Congress to grant exclusive rights to an inventor for a *limited time*. That limited time should be a definite time and, thereafter, *immediate competition should be encouraged*. For that

⁹⁹ For analysis of balancing patent law and competition law in U.S. appellate jurisprudence, see e.g., *Hotchkiss v. Greenwood* 11 How. 248, (1851); *Cuno Corp. v. Automatic Devices Corp.* 314 US 84 (1941); *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17–18 (1966); *KSR Int'l v. Teleflex, Inc.*, 550 U.S. 398, 419 (2007). For a parallel analysis in Canadian jurisprudence, see e.g., *Royal Typewriter Co. v. Remington Rand, Inc.*, 168 F.2d 691 (2d Cir. 1948); *Whirlpool Corp. v. Camco Inc.*, [2000] 2 S.C.R. 1067 (Can.); *Free World Trust v. Electro Sante Inc.*, [2000] 2 S.C.R. 1024 (Can.).

¹⁰⁰ For an articulation of the product cluster hypothesis, see e.g., Bouchard, 2010; Bouchard, R.A. *Patently Innovative. How Pharmaceutical Firms Use Emerging Patent Law to Extend Monopolies on Blockbuster Drugs*. Biohealthcare Publishing (Oxford) Limited (Oxford UK). Publication Date: Summer 2011. Online: <<http://www.amazon.com/Patently-Innovative-Pharmaceutical-Monopolies-Blockbuster/dp/1907568123>>. The term “patent clusters” was used in the “Originator-Generic Competition” Fact Sheet accompanying the EC Sector Pharmaceutical Sector Preliminary Report, where it was stated that a common strategy employed by brand firms to maintain revenue streams from blockbuster drugs for as long as possible is the creation of “patent clusters” by the filing of numerous patents for the same medicine. As noted in the report, evidence obtained by the Commission from inspections of originator companies revealed that the objective of the clustering strategy was to delay or block the market entry of generic medicines.

¹⁰¹ *Merck & Co. v. Apotex Inc.* 2009 FCA 187; *Apotex Inc. v. Merck & Co. Inc et al.*, 2008 FC 1185. For a discussion of the issue of generic compensation, see: Hollis A. “Generic Drug Pricing and Procurement” School of Public Policy, University of Calgary, Discussion paper 2(1), February 2009.

reason, Title I of the bill permits the filing of abbreviated new drug applications before a patent expires and contemplates that the effective approval date will be the expiration date of *the* valid patent covering *the* original product. Other sections of Title II permit the extension of the term of a patent for a *definite* time provided certain conditions are met. [Emphasis Added].¹⁰²

According to this argument, evergreening of older products via multiple patent listing is contrary to the objective of Hatch Waxman to facilitate generic entry via a short-term suspension of patent infringement and competition.

The Committee on the Judiciary, to whom Hatch Waxman was also referred, acknowledged that FDA rules restricting generic entry prior to Hatch Waxman “had serious anti-competitive effects” and that the “net result of these rules has been the practical extension of the monopoly position of the patent holder beyond the expiration of the patent”.¹⁰³ The Committee went further as regards the multiple patent listing issue, stating:

The first amendment rejected by the Committee was offered by Mr. Hughes. The Hughes amendment would have permitted the granting of a patent term extension for the substances regulated by the bill for each regulatory review period. *The net result of the amendment was to permit multiple patent term extensions on what was essentially the same drug product.* This amendment was supported by the Patent and Trademark Office (PTO). The PTO argued that the version of H.R. 3605 reported by the Committee on Energy and Commerce *would create two different types of patents for drugs*, those which are extendable and those which are not extendable. The latter category, they claim, includes subsequent use, method and composition patents.

The Committee considered these arguments and rejected them for two reasons. First, the *Committee accepted the rationale put forward by the Committee on Energy and Commerce concerning the need to avoid multiple patent term extensions. Our sister committee argued that the only patented product which experiences any substantial regulatory delay is the first product patent (or if there is no product patent, the first process patent).* Therefore, they reason that subsequent patents on approved drug products are frequently not the same magnitude of innovation as occurs with respect to the initial patent. Thus, the Committee on Energy and Commerce concluded on public policy and health policy grounds that only the first patent on a drug-type product should be extended. [Emphasis Added]¹⁰⁴

In making these comments, the Committee on the Judiciary stated in plain and unambiguous terms that patent extension on weakly innovative products was contrary to public policy and health policy grounds. The specific mention of the “first product patent” parallels comments made in the Parliamentary debate in Canada prior to linkage coming into force that generic entry would occur on expiry of the “main patent” on a given product,¹⁰⁵ not on expiry of a cluster of patents. This statement is coherent with that of the Committee on Energy and Commerce to the effect that the appropriate time for generic entry is the expiration date of the valid patent (or patents) covering the original product and that the Hatch Waxman amendments do not contemplate any other method of extending patent term.”¹⁰⁶

¹⁰² HR(I), at 30.

¹⁰³ HR 98-857 (II), at 4.

¹⁰⁴ *Id.*, at 5-6.

¹⁰⁵ Bouchard 2011.

¹⁰⁶ At 30, the Committee stated: article 1, section 8, clause 8 of the constitution empowers congress to grant exclusive rights to an inventor for a limited time. That limited time should be a definite time and, thereafter, immediate competition should be encouraged. For That reason, Title I of the bill permits the filing of abbreviated new drug applications before a

Later in its report, the Committee on the Judiciary was more explicit as to what public policy grounds were involved, stating that early generic availability would substantially “assist in the reduction of health care costs, particularly for the poor, the under-insured, and the elderly.” The government as a purchaser of prescription drugs was also deemed to benefit substantially by the amendments. The Committee on the Judiciary also stipulated that given the regulatory nature of the industry involved, early working allowing a shortening of the delay of generic entry between 18-24 months would not unduly encroach on the patent rights of brand firms and thus properly enhanced competition between brand and generic firms.¹⁰⁷ This is consistent with the statement of the Federal Circuit in *Mylan*¹⁰⁸ to the effect that the Hatch Waxman amendments were intended to balance two competing policy goals and that this balancing function was achieved by establishing a generic drug approval procedure at one end of the balance and restoring patent terms for pioneer firms to make up for lost time during the regulatory approval stage at the other end. No mention was made of creating a second back-end process for evergreening older drugs.

While it may not have been anticipated at the time linkage came into force in either originating jurisdiction, and bearing in mind the Committee on the Judiciary’s statement that up to *Bolar*, Congress “has never had occasion to evaluate the competing policy considerations presented by this bill,”¹⁰⁹ the empirical data that have been reported in countries with longer standing linkage regulations such as the United States and Canada suggest that the multiple patent listing mechanism has grown to be sufficiently unwieldy that the outputs of the system (delayed generic entry and anti-competitive effects) may be in increasing conflict with the twin policy goals underpinning both Hatch Waxman and the NOC Regulations. That is, that permitting multiple patent listings on an array, or cluster, of related drug products may combine to yield a system which behaves in precisely the same manner said by the Committee on the Judiciary to offend public policy and health policy grounds.

There have been numerous suggestions in case law and government reports that the multiple patent listing models was adopted because food and drug agencies such as the FDA, Health Canada and others did not, and indeed do not, have the expertise to judge patent validity and/or infringement. This sentiment was echoed in the recent *Bayer v. India* decision.¹¹⁰ The court held that drug regulators were “plainly not equipped to deal with issues concerning the validity of a patent” and that to oblige regulators to do so would be inconsistent with their mandate as regulators and the private law function of domestic Indian patent legislation. Indeed, amendments to linkage law pertaining to patent listing in jurisdictions such as the United States and Canada that have been interpreted by some to be successful¹¹¹ may be less so than recognized in the long run, if only because they have been too far downstream to be truly effective. In other words, the amendments have been aimed at fixing automatic stay abuses even though the *antecedent* problem that gives rise to these abuses is that of multiple patent listing, particularly in relation to product clusters. As noted supra, this reasoning was

patent expires and contemplates that the effective approval Date will be the expiration date of the valid patent covering the original Product. Other sections of title ii permit the extension of the term of a patent for a definite time provided certain conditions are met. There should be no other direct or indirect method of extending patent term.

¹⁰⁷ HR Rep 98-857(II), at 25.

¹⁰⁸ *Mylan Pharmaceuticals v. Bristol-Myers Squibb Co.* 268 F.3d 1323, at 1326, citing H.R.Rep. No. 98-857, pt. 1 at 14 (1984).

¹⁰⁹ *Id.*

¹¹⁰ *Bayer Corporation & Ors. v. Union of India & Ors.* LPA 443/2009, at para 28

¹¹¹ Epstein and Kuhlik 2004; Avery 2008.

employed in *Bayer* to deny linkage of food and drug law to patent law through the infringement section of India's patent legislation.¹¹²

A mechanism for oversight of patent listing that may be both more efficient and more effective than policing by the courts or drug regulators may be to create a separate administrative body within the mandate of the PTO to independently assess patents for relevance to new and innovative drugs prior to listing, as occurs in some jurisdictions with regards to drug price controls. Similar arm's length institutions have been created to police drug prices in Canada (Patented Medicines Prices Review Board, or PMPRB)¹¹³ and to facilitate translational research and innovative drug development in the United States (National Center for Advancing Translational Sciences).¹¹⁴

Finally, we note that there appears to be significant cultural differences between jurisdictions as to the tendency of both brand and generic firms to game the system and the reaction of the public and government when the system is effectively gamed. Jurisdictions such as the United States that are viewed by some to have more of an arm's length relation between government and industry and be comparatively more litigious in seeking legal remedies,¹¹⁵ may exhibit faster and more efficient adaptive responses than jurisdictions with more cooperation between government and industry. As indicated by the rapid and strong responses of nations such as India and Australia to the push for linkage in those jurisdictions compared to the more receptive responses of nations such as Canada, Mexico and South Korea, it is possible there are significant cultural differences in the manner in which linkage is accepted or refuted and, when it is accepted, the speed and strength of adaptive responses by law-makers when the system is acknowledged to list to one side and require correction. A similar conclusion may be drawn with regard to the comparative responses of the public and governments of the United States and Canada in response to perceived abuses of the automatic stay provision.

The goal of this leg of our research will be to obtain empirical qualitative and quantitative data to determine whether or not multiple patents listed per drug provide the linchpin for a potential clustering effect of this nature. As revealed by the recent E.C. Pharmaceutical Sector Inquiry, the Bolar debate is far from over: some originator firms are claiming that by permitting marketing authorization before a patent dispute has been settled, "the authorities willingly collude in the alleged patent infringement".¹¹⁶ The argument is not persuasive, but nonetheless may carry weight with some regulators.

¹¹² *Bayer Corporation & Ors. v. Union of India & Ors.* LPA 443/2009.

¹¹³ <http://www.pmprb-cepmb.gc.ca/english/home.asp?x=1>

¹¹⁴ Harris, G. Federal Research Center Will Help Develop Medicines. *New York Times*. January 22, 2011. Online: <<http://www.nytimes.com/2011/01/23/health/policy/23drug.html?ref=health>>.

¹¹⁵ Witorowitz 2004.

¹¹⁶ EC Pharmaceutical Sector Final Report, at 315: "Certain originator companies allege that by granting marketing authorisation, the authorities willingly collude in the alleged infringement. These originator companies therefore argue that no marketing authorisation should be granted until the allegation of patent infringement has been settled. Occasionally, actions are accompanied by a threat to sue the marketing authorisation body for damages if marketing authorisation is granted." At para 260 of its Preliminary Report, it is stated that "As long as these activities are strictly necessary to prepare for an MA application, they are not deemed to infringe patents rights ... for medicinal products in view of the so-called Bolar provision. This provision, which was introduced by Directive 2004/27, creates a safe harbour for certain tests and studies while the reference product is still patent-protected so as to enable the generic producer to apply for marketing authorisation once the eight-year period of data exclusivity granted to the holder of the original MA has elapsed."

B. *Legal Checks and Balances*

In addition to identifying the original starting conditions for linkage, it is also important to map the system of legal checks and balances in different linkage regimes and investigate how they operate together to determine the outputs of the system. The specific basket of checks and balances in a given linkage regime is vital, as it determines not only how a complex system of pharmaceutical regulation begins operating *de novo* following the coming into force of law but also how it evolves over time to yield demonstrable empirical results. It has been shown, for example, that the behavior of dynamic legal systems,¹¹⁷ including how systems learn, self-regulate, adapt and grow,¹¹⁸ is strongly influenced by positive and negative feedback.¹¹⁹ Positive feedback results in growth or amplification of a particular process or group of related processes whereas negative feedback results in tamping or slowing of a particular process or group of processes. Studies of complex social, biological and technological systems have shown that the unintended consequences resulting from feedback has the potential to force a system away from operating at or near the point of efficiency.¹²⁰

In the case of linkage regulations, unchecked feedback could yield an array of results that move the system away from its intended consequences. For example, even though the original policy intent was to balance production of new and innovative drugs with timely generic entry, a poorly operating system could yield a decline in innovative products despite strong patent protection; substantial delays in generic entry despite abbreviated procedures for approval; increased monopoly pricing; wasteful litigation; and increased public health costs. Results such as these could be the consequence of a system with insufficient checks and balances that is driven to certain outputs much like damage to one wheel forces a car to inevitably list to one side.

An example of feedback with unintended consequences is provided for by the automatic stay, which is a fundamental feature of pharmaceutical linkage. Studies in both North American jurisdictions where linkage originally came into force have demonstrated that that the likelihood of further patent listing and litigation on high value drugs increases substantially when a brand firm experiences success with its first stay.¹²¹ Given the automatic nature of the injunction, generics can be kept off market with comparatively less risk to

¹¹⁷ Harrison 1997; Jervis 1997.

¹¹⁸ J.B. Ruhl. "The Fitness of Law: Using Complexity Theory to Describe the Evolution of Law and Society and its Practical Meaning for Democracy" (1996) 49 Vand. L. Rev. 1407; JB Ruhl. "Regulation by Adaptive Management: Is It Possible?" (2005) 7(1) Minnesota Journal of Law, Science and Technology 21.

¹¹⁹ See generally Albert-László Barabási, *Linked: How Everything is Connected to Everything Else and What It Means for Business, Science, and Everyday Life* (Plume 2003); James Gleick, *Chaos: Making a New Science* (New York: Penguin, 1988); John H. Holland, *Adaptation in Natural and Artificial Systems* (MIT Press, 1992); John H. Holland, *Hidden Order: How Adaptation Builds Complexity* (Basic, 1995); Steven Johnson, *Emergence: The Connected Lives of Ants, Brains, Cities, and Software* (Scribner, 2002); Stuart Kauffman, *At Home in the Universe: The Search for the Laws of Self-Organization and Complexity* (Oxford University Press, 1995); Gregoire Nicolis & Ilya Prigogine, *Exploring Complexity: An Introduction* (New York: W.H. Freeman and Company, 1990); M. Mitchell Waldrop, *Complexity: The Emerging Science at the Edge of Order and Chaos* (New York: Simon & Schuster, 1992); Brian W. Arthur, "Positive Feedbacks in the Economy" (1990) 262 Scientific American 92, 92-99.

¹²⁰ See, e.g., Robert M. May et al., "Complex Systems: Ecology for Bankers" (2008) 451 Nature 893. For a look at the role of feedback in policy failure, see generally Jervis, 1997; Harrison, 1997; Bozeman, 2002; Bozeman & Sarewitz, 2005; and Serman, 2002; Bouchard, R.A., "Reflections on the Value of Systems Models for Regulation of Medical Research and Product Development" (2008) 17(1) Health Law Review 28-43; Bouchard, R.A., "KSR v. Teleflex Part 2: Impact of U.S. Supreme Court Patent Law on Canadian and Global Systems-Based Innovation Ecologies" (2008) 15(1) Health Law Journal 247-293.

¹²¹ FTC Study 2002; Caffrey and Rotter 2003; Bulow 2003; Hore 2004; Avery 2008.

brand firms.¹²² As noted by the Federal Court of Canada,¹²³ which exclusively hears patent matters under the NOC Regulations, “by merely commencing the proceeding, the applicant obtains what is tantamount to an interlocutory injunction for up to 30 months without having satisfied any of the criteria a court would require before enjoining issuance of an NOC.”

The delay of generic entry owing to abuses of the automatic stay is just one example of unintended consequences of legislation that occur as a result of adaptation by firms as they gain experience with the system of legal checks and balances that comprise a particular linkage regime. Our work has identified a number of differences in the system of checks and balances employed by different jurisdictions. It also suggests that feedback between these mechanisms can strongly influence the output of the system on brand and generic drug availability and costs.

For example, the U.S. Hatch Waxman Act regime provides generic firms with the opportunity to early-work an invention without infringing brand patents (Bolar) as well as to indirectly rely on the data in the branded company’s application to support a generic company’s application for approval. These benefits are balanced however, by the automatic stay of 30 months in favor of brand firms, which can be shortened or lengthened at the discretion of a court. A court’s early determination of patent invalidity or non-infringement will necessarily cut the 30 month period short. On a secondary level, the 30 month stay preventing generics from entering the market is balanced by 180 day period of marketing exclusivity for the first entrant where generic prices could escalate in absence of further generic competition. The intent of this 180 day exclusivity period is to provide an incentive to challenge patents. This series of legal checks and balances should in theory minimize strong positive feedback in favor of either brand or generic firms, and works towards balancing the interests of both parties as well as the competing policy goals involved.¹²⁴ In practice there has been significant gaming of the automatic stay which has led to frequent settlements between generics and brands.¹²⁵

Unlike the United States, Canada had a significant generic industry prior to the linkage regime. Repeal of compulsory licensing and the coming into force of the NOC Regulations was intended to balance the competing interests of brand and generic drugs and to effect cost savings for consumers. As in United States, both a Bolar provision and 30 month stay (now reduced to 24 months) were provided under the linkage regime. However, unlike the United States, the automatic stay in Canada was not balanced by any exclusivity period for generics and the incentives for generic entry are relatively weak.¹²⁶ At the same time, generic

¹²² In the U.S., the risk is also minimized for generics, who can resolve patent issues without risking damages incurred in marketing the drug and then being sued for infringement. This is not the case in Canada, as proceedings under linkage laws are summary in nature and can, and often are, followed by full infringement proceedings. A recent study of litigation in the E.U. (EC Pharmaceutical Sector Final Report) revealed that even when disputes are few in number, they exert a strong chilling effect on generic entry as a result of the mere *risk* of interim injunctions. The data showed that over half of proceedings against generics were preceded by prior disputes, leading the authors to conclude the chilling effect of even a small number of proceedings “illustrates the strength of the link between patent-related exchanges and patent litigation.”

¹²³ *AstraZeneca v. Apotex, Minister of Health* 2004 FC 1277.

¹²⁴ Mossinghoff 1999.

¹²⁵ FTC Study 2002. See also: Federal Trade Commission, “Pay-for-Delay. How Drug Company Pay-Offs Cost Consumers Billions” (January 2010), online: Federal Trade Commission <<http://www.ftc.gov/os/2010/01/100112payfordelayrpt.pdf>>.

¹²⁶ Hollis A. “Generic Drug Pricing and Procurement” School of Public Policy, University of Calgary, Discussion paper 2(1), February 2009.

firms are limited in the damages they can collect if they are excluded from the market on the basis of brand litigation on an invalid patent.¹²⁷ Moreover, unlike the U.S. regime, proceedings under the NOC Regulations are summary in nature and do not constitute a final decision on issues of validity or infringement. Thus, even under circumstances where a generic has obtained a finding of invalidity or non-infringement on all relevant listed patents, it is still vulnerable to a traditional infringement action on the same patents. By contrast, the provision for generics to challenge patents prior to marketing and eliminate the threat of infringement is a prime mechanism by which the U.S. Hatch Waxman regime is seen to foster generic entry. Were it not for the combination of both mechanisms, linkage was seen to operate only as a type of advisory option given the vulnerability of generic firms to double-jeopardy type litigation. Therefore, unlike the U.S. regulations, the specific system of legal checks and balances inherent to the Canadian linkage system may provide for greater legal uncertainty and list, unintentionally, to the side of brand pharmaceutical firms.¹²⁸

Australia, by contrast, seems to have learned and adapted well from these experiences. Australian trade negotiators, for example, included in the domestic linkage regime specific provisions against evergreening and a provision for evidence-based assessment of pharmaceutical innovation despite opposition from American negotiators.¹²⁹ Analogous to the U.S. regime, this provision has been balanced by more recent changes to domestic formulary law mandating price controls for generic drugs under certain circumstances. India's patent legislation also contains a provision against evergreening, which has been challenged unsuccessfully by brand firms as being non-compliant with TRIPS.¹³⁰

C. Convergence of Public Health and Economic Policy

The original policy intent to balance the competing goals of stimulating pioneering innovation and facilitating generic entry through the same legal nexus necessarily implies a certain degree of policy disharmony. The first of these goals is aimed primarily at private gain while the second is to public gain in the form of lower government expenditures and/or lower costs to consumers. While in practice both brand and generic firms seek to increase market share for their own ends, the goal of cost savings renders increased generic availability an important public health issue.¹³¹ This has not gone unnoticed by the Supreme Court of Canada in its assessment of the nation's linkage regime.¹³² Similar observations have been made by the United States Supreme Court.¹³³ It is clear in both jurisdictions that convergence of public health and economic policy has been embraced, however reluctantly, in the form of the linkage regime as well as other legislation relating to prioritization and

¹²⁷ *Merck & Co. v Apotex Inc.* 2009 FCA 187; *Apotex Inc. v Merck & Co. Inc et al.*, 2008 FC 1185.

¹²⁸ Hollis A, "Generic Drug Pricing in Canada: Components of the Value-Chain." University of Calgary Department of Economics Working Paper 2010-10, May 2010.

¹²⁹ Faunce TA, et al. "Assessing the Impact of the Australia-United States Free Trade Agreement (AUSFTA) on Australian and Global Medicines Policy" (2005) 1 *Globalisation and Health* 1–15.

¹³⁰ Section 3(d) of the Indian Patents Act, 1970. For a description of Indian patent law in the context of pharmaceuticals, see Khader, Feroz Ali, *The Law of Patents-With a Special Focus on Pharmaceuticals in India* (India: LexisNexis Butterworths, 2007).

¹³¹ Roy J. Romanow Commission on the Future of Health Care in Canada, *Building on Values: The Future of Health Care in Canada* (Ottawa: Public Works and Government Services Canada, 2002); Senator Hatch, at the time the legislation came into force said "The public receives the best of both worlds – cheaper drugs today and better drugs tomorrow". Congressional Record – Senate at 23764 (August 10, 1984).

¹³² *Merck Frosst Can. Inc. v Canada*, [1998] 2 S.C.R. 193; *AstraZeneca Can., Inc. v Canada*, [2006] S.C.R. 560, 2006 SCC 52; *Bristol-Myers Squibb Co. v Canada*, [2005] 1 S.C.R. 533 SCC 26.

¹³³ *Eli Lilly & Co. v Medtronic, Inc.*, 496 U.S. 661, 676-679 (1990).

commercialization of publicly funded medical research (cf. Fig. 1).¹³⁴ For example, in *AstraZeneca v. Canada*,¹³⁵ the Supreme Court of Canada recently held that pharmaceutical linkage lies “at the intersection of two regulatory systems with sometimes conflicting objectives.” Whereas food and drug law seeking to ensure the safety and efficacy of new medications before they can be put on the market, patent law provides private inventors with exclusive right to exploit their invention for a period equal to the patent term. Regarding the convergence of public health and economic, or industrial, law, the court noted that until linkage came into force the two regulatory systems were largely kept “distinct and separate.”

Other jurisdictions, however, have not heeded the siren call of convergence. For example, in the recent High Court of Delhi *Bayer* decision,¹³⁶ the court rejected linkage specifically on the grounds of convergence. Justice Muralidhar, speaking for the Court, stated that the legislative schemes for patent law and drug approval are “distinct and separate” and that any attempt to establish a linkage between the two cannot be countenanced.¹³⁷ The court noted that in granting approval for generic equivalents, drug regulators neither per se infringe the patent rights of brand firms nor abet the infringement of such rights by generic firms simply because the drug is patented.¹³⁸ In rendering its decision, the court noted that given the presumption of validity for patents associated with the drug for which marketing approval is sought, linkage would improperly oblige drug regulators to enforce the rights of owners under patent legislation, which is not the function of the regulator.¹³⁹ The court held that such action was in the private law domain, and that when a private right is conferred by a statute such as under domestic patent legislation, the proper remedy for an infringement of that right must be in terms of that statute and no other. The court noted that the expectation is that the patent holder will institute appropriate infringement proceedings under patent law when it deems its rights to be infringed, and that patentees do not require the help of drug regulators to do so. For these reasons, pharmaceutical linkage was held to contravene the government’s interest in public health by rendering patented drugs unaffordable and non-accessible.¹⁴⁰ Bayer appealed to the Supreme Court of India, which Court dismissed Bayer’s appeal based on its finding that the decision of the High Court of Delhi was well-reasoned and without error.¹⁴¹

¹³⁴ Krinsky 2003.

¹³⁵ *AstraZeneca Can. Inc. v. Canada*. [2006] 2 S.C.R. 560, ¶ 12 (Can.).

¹³⁶ *Bayer Corporation & Ors. v. Union of India & Ors.* LPA 443/2009.

¹³⁷ *Id.* At para 28, Justice Muralidhar stated: “This Court concurs with the learned Single Judge that the scheme of both the Patents Act and the DCA are distinct and separate and that the attempt by the appellant Bayer to establish a linkage cannot be countenanced.” What Bayer wants the DCGI to do is to enforce its rights as a patent holder in terms of Section 48 of the Patents Act. That is plainly not the function of the DCGI. His powers and jurisdiction are circumscribed by the DCA and not the Patents Act. It is entirely up to the patent holder to seek whatever remedies are available to it to enforce and protect its patent from infringement. This is in the private law domain. The DCA has nothing to do with it. There is merit in the contention that when a private right is conferred by a statute, the remedy for an infringement of that right has to be in terms of that statute and no other.” At para 29, the court further stated: “The expectation is that the patent holder will institute appropriate proceedings during the “monopoly” period to safeguard its rights in terms of Section 48 of the Patents Act. It does not require the DCGI’s help in this.”

¹³⁸ *Id.*, at para 22 and 25.

¹³⁹ *Id.*, at para 28

¹⁴⁰ *Id.* at para 30: “There is considerable literature on the topic with many a developing country resisting it in the interests of public health care that is both affordable and accessible”.

¹⁴¹ *Bayer Corporation & Ors. v. Union of India & Ors.* SLP 6540/2010.

While one can look at India primarily as a jurisdiction with strong generic interests, the same cannot be said of the European Union, where many global pharmaceutical firms are based. In its 2009 Final Report of the Pharmaceutical Sector Inquiry, the E.C. stipulated that under E.U. law regulatory approval is not linked to patent status, nor can same be used to refuse, suspend or revoke marketing authorization.¹⁴² Echoing the decision of the High Court of Delhi in *Bayer*, the Commission specified that “the task of marketing authorisation bodies is to verify whether a medicinal product is safe, effective and of good quality. Their main function is to ensure that the pharmaceutical products reaching the market are not harmful to public health. Other factors, such as the patent status of the product, should therefore not be taken into account when assessing the risk/benefit balance of a medicine.” While this precedent has been followed in Italy,¹⁴³ the Mexican Supreme Court recently held that the main function of pharmaceutical linkage is explicitly for the regulatory authority to reject marketing authorizations that violate patent rights.¹⁴⁴

Based on the variability of the approach in different jurisdictions to the practice of policy convergence, it is unclear but important what advantages, if any, regulatory authorities have – or should have - over the courts in terms of policing violations of patent rights. As such, this is a fruitful area for future research for scholars as well as key decision-makers.

D. Expansion of Linkage Beyond the Drug Approval-Drug Patenting Nexus

There is growing recognition that the system of pharmaceutical linkage regulation is aggressively expanding not only globally,¹⁴⁵ but also in scope.¹⁴⁶ This expansion has the potential to significantly impact domestic systems of intellectual property, but may also strongly influence the movement of drugs between nations intended for humanitarian purposes. We will investigate the expansion of pharmaceutical linkage in different jurisdictions as well as the legal mechanisms and policy grounds underpinning this evolution.

¹⁴² At p. 261 (para 714), the European Commission Pharmaceutical Sector Preliminary Report 2008 states that “Article 81 of Regulation (EC) 726/2004 and Article 126 of Directive (EC) 2001/83 provide that an authorisation to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in the Regulation and the Directive. Considering that patent status is not included in the grounds set out in the Regulation and the Directive, it cannot be used as an argument to refuse, suspend or revoke a marketing authorisation. The Commission may launch infringement proceedings against any Member State which infringes the Directive.” Similarly, in South Korea, the drug approval authority does not take into account the patent status on the ground that the drug approval authority is not competent to do so. Only when a court confirms a patent infringement, the drug approval is cancelled ex post (Article 43(7) (previously Article 40(1)(8)) of the Enforcement Regulations of the Pharmaceutical Affairs Act).

¹⁴³ Daniela Ampollini. “Patent protection irrelevant for inclusion of generics in transparency list, says the Italian Supreme Administrative Court”. In a decision of 29 July 2010, the Italian Supreme Administrative Court (Consiglio di Stato) dealt with the issue of whether the Italian drugs regulatory authority (Agenzia Italiana del Farmaco – AIFA) should consider the existence of patents when making decisions relating to the marketing authorisation of generics. The Supreme Administrative Court reversed the decision of first instance and held that the existence of a patent is irrelevant to the inclusion of an equivalent drug into a transparency list. Kluwer Patent Blog, online: <http://kluwerpatentblog.com/2010/09/08/patent-protection-irrelevant-for-inclusion-of-generics-in-transparency-list-says-the-italian-supreme-administrative-court/?utm_source=feedburner&utm_medium=email&utm_campaign=Feed%3A+KluwerPatentBlogFull+%28Kluwer+Patent+Blog+-+Latest+Entries%29>.

¹⁴⁴ Mexican Supreme Court, Thesis Contradiction 386/2009, at page 61. See also: Juan Luis Serrano. Mexican Supreme Court Decides on Broad Interpretation of Linkage Regulations (9 March 2010), online: Patent Docs Blog <<http://www.patentdocs.org/2010/03/mexican-supreme-court-decides-on-broad-interpretation-of-linkage-regulations.html>>.

¹⁴⁵ Correa, 2006; Ruiz, 2006.

¹⁴⁶ EC Pharmaceutical Sector Preliminary Report; EC Pharmaceutical Sector Inquiry Final Report.

The recent E.C. Report of the Pharmaceutical Sector Inquiry is a case in point.¹⁴⁷ The report represents the first clear articulation of policy reasons in opposition of linkage from a major economic region. It also clearly outlines an expansive legal concept of pharmaceutical linkage. The Preliminary Report, issued in November 2008 provided a list of existing and emerging patent linkages inherent to what the Sector described as a “tool-box of instruments and measures for how to prepare for and react to generic entry.” These include linkage of patent status to: contacts, disputes and litigations between originator and generic companies; opposition procedures and appeals before patent offices; patent settlements and other agreements between originator and generic companies; promotional activities, including an emphasis on follow-on and other second generation products; as well as a range of interventions by brand firms before national authorities pertaining to marketing authorization, drug pricing and reimbursement.¹⁴⁸

An evolving landscape such as this raises the question of whether the pharmaceutical industry is using linkage as an expansive tool not only to reach across national borders, but also to leverage accepted notions of linkage into a broader spectrum of regulated activities.

E. Rights Layering v. Single Point Mechanism for Incenting Innovation

Emerging empirical data on linkage regulations,¹⁴⁹ particularly when taken in combination with historical studies of patent protection for pharmaceuticals,¹⁵⁰ have demonstrated a growing sophistication of pharmaceutical firms to layer patent and other intellectual property rights on pharmaceutical products at numerous stages of development. When combined with conventional patent law and the evidentiary requirements for new and follow-on drug approval, linkage regimes provide a powerful tool for multinational pharmaceutical firms to efficiently and effectively identify attractive both new and follow-on drug candidates for prolonged market exclusivity.

The linkage regime in particular has proven to be a valuable vehicle for firms to obtain enhanced legal protection on drugs at all stages of development, including drugs about to come off patent protection, drugs moving through the regulatory approval stage, and drugs

¹⁴⁷ EC Pharmaceutical Sector Final Report (at 23) states: “The Commission will continue to strictly enforce the applicable Community law and, for instance, act against patent linkage, as according to Community legislation, marketing authorisation bodies cannot take the patent status of the originator medicine into account when deciding on marketing authorisations of generic medicines.” In the Preliminary Report, the E.C. stated (at p. 14) more specifically that Patent-linkage is considered unlawful under Regulation (EC) No 726/2004 and Directive (EC) No 2001/83. At p. 113, further elaboration is provided to the effect that: “Patent linkage refers to the practice of linking the granting of MA, the pricing and reimbursement status or any regulatory approval for a generic medicinal product, to the status of a patent (application) for the originator reference product. Under EU law, it is not allowed to link marketing authorisation to the patent status of the originator reference product. Article 81 of the Regulation and Article 126 of the Directive provide that authorisation to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in the Regulation and the Directive. Since the status of a patent (application) is not included in the grounds set out in the Regulation and in the Directive, it cannot be used as an argument for refusing, suspending or revoking MA.”

¹⁴⁸ EC Pharmaceutical Sector Preliminary Report, at 22-23 (para 9). At para 895, the report states “- including intervention before regulatory bodies. Interventions before regulatory bodies (marketing authorisation authorities and pricing and reimbursement bodies) appear to be a standard tool in originator companies’ toolbox. Although contacting the health authorities may address legitimate concerns, it can also be used to delay or block the marketing authorisation or the pricing or reimbursement status of the generic product. In particular, by suggesting that the generic product is less efficient or safe or is not equivalent, raising patent infringement issues concerning the generic product in question and alleging that any decision favourable to the generic company would make the authorities liable to patent infringement damages (patent linkage), originator companies gain time and can create delays in granting marketing approval for the generic product and its entry into the market.”

¹⁴⁹ Sawicka & Bouchard 2008; Bouchard 2009; Bouchard 2010; Hemphill and Sampat, 2011; Hemphill and Lemley 2011.

¹⁵⁰ For review, see: Boldrin & Levine 2008; Bessen & Meurer 2008.

that are currently in development.¹⁵¹ The number and array of patent types, the speed of patent listing, the automatic injunction, and the low relevance requirement for listing combined with low evidentiary requirements for new and follow-on drug approval enable pharmaceutical firms to rapidly identify attractive drug targets for legal protection both during and after regulatory approval. Added to this is the data exclusivity regime which, depending on the country being considered, now provides for up to 11.5 years of market exclusivity for products based on the confidentiality of regulatory submission data.¹⁵² When gauged against reports indicting declining levels of innovation in the pharmaceutical industry,¹⁵³ be it from a loss of low hanging fruit,¹⁵⁴ increasing research and development costs,¹⁵⁵ or firms aiming *ex ante* at legal targets offering high reward for low risk drug development,¹⁵⁶ the question arises of whether numerous layers of intellectual property protection, and the corresponding extension of market exclusivity, are encouraging or stifling innovation in the pharmaceutical sector.¹⁵⁷

It may be that one, not both, mechanisms for protecting innovative drugs will prevail in the long run. For example, in its review of patent term extension under Hatch Waxman, the United States Congressional Budget Office noted that shortening of drug review times may be a more effective means of stimulating innovative research rather than further lengthening patent protection,¹⁵⁸ since millions of dollars in sales are lost for each extra day a drug stays in the approval process. Given that review times have declined substantially over the last two decades globally,¹⁵⁹ one could ask what is the public interest in expanding patent terms via the linkage regime either alone or concomitant with data exclusivity and patent term restoration? Is it in the public interest to continue to link drug approval with patent protection to produce multiple layers of exclusivity protection? Does the convergence mechanism hold up if the economic goals of linkage are not being met? These questions are vital from a public health perspective, as the growing data exclusivity regime is a nearly perfect substitute for patent linkage, and how a given nation addresses each will impact generic entry and thus cost savings and access to essential medications.

F. Role of Empirical Studies for Public Health Systems

There is also to consider the thorny issue of the relevance of empirical research on pharmaceutical patents for the making of law and policy *ex ante* as well as its *ex post* review.

¹⁵¹ Bouchard 2010

¹⁵² Alex Stack. Canada: Trade-Driven Changes Coming to Canadian Patent and Data Protection Laws? Canada-European Union Trade Negotiations. Mondaq Intellectual property Blog. 24 September 2010. online, <<http://www.mondaq.com/canada/article.asp?articleid=106048>>

¹⁵³ *Reinventing Innovation and Commercialization Policy in Ontario* (Institute for Competitiveness & Prosperity Working Paper No. 6., 2004); Brian Guthrie & Trefor Munn-Venn, Conference Board of Canada, *Six Quick Hits for Canadian Commercialization: Leaders' Roundtable on Commercialization* (2005); Canadian Government. Rotman Expert Panel on Commercialization, *People and Excellence: The Heart of Successful Commercialization* (2006); Erika Fitzpatrick. *Innovation America: A Final Report*. National Governors Association. (2002); The Council on Competitiveness. *Innovate America: Thriving in a World of Challenge and Change* Washington, DC. (2006); The Council on Competitiveness. *Five for the Future*. Washington, DC. (2007).

¹⁵⁴ Fredric J. Cohen, *Macro Trends in Pharmaceutical Innovation*, 4 NATURE REVS. DRUG DISCOVERY 78, 82 (2005).

¹⁵⁵ Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003).

¹⁵⁶ Bouchard 2009.

¹⁵⁷ Bouchard 2010.

¹⁵⁸ Glasgow 2001, at 257 note 174 and 175, citing Information Access Company, "Debate on Patent Extension Intensifies" (1999) 21 Chain Drug Review. RX82

¹⁵⁹ For review of the relevant literature, see: Joel Lexchin, "Drug Withdrawals from the Canadian Market for Safety Reasons, 1963–2004" (2005) 172 Canadian Medical Association Journal 765; Bouchard, R.A. & Monika Sawicka, "The Mud and the Blood and the Beer: Canada's New Progressive Licensing Framework for Drug Approval" (2009) 3(1) McGill Journal of Law & Health 85-119.

Indeed, there is a growing discordance between the policy grounds underpinning the pharmaceutical linkage and the results of empirical studies intended to assess their effectiveness as well as that of the patent system more generally in providing incentives for innovation. As noted above, the goal of the linkage regime is often cited as balancing the conflicting policy goals of facilitating the development of new and innovative drugs and timely generic entry. We have recently completed a number of studies that empirically assessed the impact of linkage regulations on drug approval for new and follow on drugs, the degree of innovation associated with the products, drug patenting and associated litigation, and the extension of market exclusivity on blockbuster products coming off patent due solely to linkage.¹⁶⁰

The results of empirical studies such as these have profound ramifications for assessment of how well the linkage regime is working as currently constituted and thus enables conclusions as to the *vires* of legislation when gauged against its original policy goals. We found, for example, that loopholes in linkage laws as they operate in tandem with low evidentiary requirements for drug approval can provide for clustering of follow-on drugs and related patents, and that these clusters of drugs and patents can substantially extend the cumulative patent life of older blockbuster drugs by as much as a factor of two.¹⁶¹ Even when one only takes into consideration the extension of market exclusivity observed when all relevant patents listed on the patent register have been litigated and found to be invalid or not infringed, operation of linkage delays generic entry by 3-5 years. This can be compared to the 7 month (weighted average) delay for generic entry following the loss of patent protection in the European Union in the absence of linkage.¹⁶² The E.C. Pharmaceutical Sector Inquiry recently found that savings due to generic entry on medications studied over the period 2000 to 2007 would have been 20% greater if entry had taken place immediately following the loss of brand exclusivity.¹⁶³ Thus, the lag between the loss of brand exclusivity and generic entry, and the contribution thereto by linkage laws, is critical for public health savings from a qualitative as well as quantitative perspective.

In addition to obtaining data pertaining to drug approval, litigation and innovation, it will be necessary to investigate the relationship of this data to those for sales and profit data before and after linkage regulations came into force, the fractional cost of generics at different points in the product lifecycle compared to brand products across jurisdictions, as well as how linkage regulations in different jurisdictions determine the duration of market exclusivities and their impact on the price of brand and generic drugs, particularly before and after litigation under various linkage provisions has terminated. The growing cache of empirical data on pharmaceutical linkage may be of increasing importance, as numerous jurisdictions worldwide are in the process of revising, rejecting or bringing in pharmaceutical linkage regulations. Empirical evidence as to the successes and failures of different forms of linkage would therefore be valuable, both domestically and globally.

Discordance between claims for pharmaceutical linkage and the so-called “real world” effects of linkage on drug development are not new. For example, in the political debate leading up to repeal of compulsory licensing and the coming into force of the Canadian regulations, an evidence-based approach to drug patenting and pharmaceutical linkage was

¹⁶⁰ For a review of these studies, see: Bouchard 2011.

¹⁶¹ Bouchard 2009

¹⁶² EC Pharmaceutical Sector Report Final, at p. 8 (para 2, 2.1.2).

¹⁶³ Id, at p. 9 (para 3, 2.1.2.)

rejected by Parliament.¹⁶⁴ During the hearings, a U.S.-based economist specializing in drug development gave evidence as to the importance of empirical studies when assessing linkage regulations, suggesting that a Hatch Waxman-like linkage regime would enhance market exclusivity for blockbuster drugs several-fold more than anticipated to the detriment of payers in the absence of demonstrable increases in national research and development capacity. The evidence was that multiple patents per drug would be affected and that the average delay for generic entry would be on the order of 10-15 years.¹⁶⁵ The data were discounted in favor of the unsupported claim that only one patent per drug would be affected and that the average delay in generic entry would be minimal and the tacit assumption that increased patent protection would yield both increased innovation and public welfare.¹⁶⁶ There appeared to be no middle ground during the negotiations or a reasonable appreciation for the value of empirical data to the debate.¹⁶⁷ A similar situation evolved in the United States following the coming into force of Hatch Waxman, and was addressed in subsequent amendments to the legislation.¹⁶⁸

Data from our early work on global pharmaceutical linkage indicate that the debate over the value of empirical data for law-making relative to linkage regulations is far from over and indeed may be taking on new relevance. Jurisdictions that were not ready during the original debates over linkage to address what may have been seen as an isolated study¹⁶⁹ are now

¹⁶⁴ During the lead up to repeal of Canada's compulsory licensing and the coming into force of the NOC Regulations, both the Canadian Medical Association and Canadian Consumers Association requested that the federal government take an "evidence-based" approach to assessing research and development costs and the impact of patent reforms on the costs and benefits of the public health system. CMA, Legislative Committee, *supra* note 6, at 4:8, 4A:18 and 4:10, and CCA Legislative Committee, *supra* note 6, at 5:53. Harrison, *supra* note 4, at 526, concluded in his study of the political and economic factors underpinning Bill C-22 and Bill C-91 that "one cannot persuasively argue that the Mulroney administration tied or linked this costly policy (repeal of compulsory licensing) to any tangible benefit." Indeed, during the debate over repeal of compulsory licensing and patent reforms in the lead up to TRIPS, NAFTA and Bill C-22, proponents of increased patent protection were criticised for the lack of commitments by the pharmaceutical industry that would be "measurable and enforceable". The Minister of Consumer and Corporate Affairs at the time, Harvie Andre, replied that output metrics were not necessary, saying instead "We prefer carrots to whips. If it turns out that the donkey will not go with the carrot then maybe you will have to use the whip". (Parliament of Canada, 33:2, Minutes of Proceedings and Evidence of the Legislative Committee on Bill C-22. December 16, 1982, 1:11, 1545 and 1625.

¹⁶⁵ Tancer, 1997; Harrison, 1997; Bouchard 2011.

¹⁶⁶ Bouchard, *Id.*

¹⁶⁷ *Id.*

¹⁶⁸ Epstein & Kuhlik 2004; Avery 2008. It was recognized as early as 2001 that pharmaceutical patent reforms such as linkage regulations could extend the average patent life of pharmaceuticals by at least 50% (Glasgow, at 233 note 27, citing at RX13.Gale Group at note 19). In its 2002 report, the FTC reported that 50% of patents listed in the Orange Book (US patent register) were either invalid or not infringed by generic products (FTC Study,2002), suggesting that undue prolongation of patent monopolies under Hatch Waxman Act constituted abuses of linkage law. Two years later, the U.S. Congressional Budget Office noted that the number of new pharmaceutical products was declining even as patent protection for pharmaceuticals was escalating (CBO. Research and development in the pharmaceutical industry. Note 8 in Kesselheim). Results such as these prompted Kesselheim & Avorn to note in 2006 that growing legal exclusivity periods in the pharmaceutical sector had already produced a wide range of negative effects on public health, including making essential medications unaffordable to developing nations, preventing dissemination of patented processes for vitamin fortification to underserved populations, limiting the ability of nations to manage epidemics, releasing new drugs only as combination therapies to avoid generic entry, and the inflation of drug prices generally (Kesselheim & Avorn, *Journal of the American Medical Association* (2006) 434-437, at 434).

¹⁶⁹ For review of interpretation of Dr. Schondenmeyer's data in the Canadian context, see: Robert Tancer, "Foreign investment in North America and the Pharmaceutical Industry in Canada" (1997) 39(2) *The International Executive* 283-297; Donald G. McFetridge. Intellectual property rights and the location of innovative activity: The Canadian experience with compulsory licensing of patented pharmaceuticals. NBER Paper. July 29, 1997. Christopher Scott Harrison, "Protection of Pharmaceuticals as Foreign Policy: The Canada-U.S. Trade Agreement and Bill C-22 versus the North American Free Trade Agreement and Bill C-91", (2001) 26 *N.C. Int'l L. & Com. Reg.* 457-528; Bouchard 2011.

faced with mounting empirical work on pharmaceuticals and patents,¹⁷⁰ including linkage.¹⁷¹ A second conclusion is that jurisdictions outside North America appear to have taken lessons from those with previous experience more seriously in bringing in or rejecting domestic versions of linkage. An important issue to explore is what factors were seen by various jurisdictions as more or less important in their linkage deliberations and what the likely reasons were for others to ignore these lessons? Moreover, what lessons were drawn from studies of the outputs from different systems of checks and balances in various jurisdictions, and how did these lessons inform the customization of pharmaceutical linkage in various jurisdictions?

Consider, for example, the comparative linkage experience in the European Union, Australia and South Korea. South Korea is in the midst of ratifying a FTA with the United States that includes provisions for linkage.¹⁷² As part of its deliberations, the South Korean government produced a study claiming to assess the impact of the linkage regime on research and development, drug costs and job creation.¹⁷³ The results of this study were not positive from a social welfare perspective.¹⁷⁴ Of interest, however, the study appears to ignore empirical data from more recent American and Canadian studies, instead making errors of assumption similar to those made at the time the Canadian regime came into existence over twenty years ago.

This can be compared with studies conducted by Australian and E.U. governments, both of which demonstrated significant learning from past experience and strong adaptation. Data obtained by the European Union was broad in scope, depth and balance of analysis,¹⁷⁵ and thus well informed linkage policy and law. After intense deliberation and public debate,¹⁷⁶

¹⁷⁰ Boldrin & Levine, 2008; Bessen & Meurer, 2008. See also: Adam Jaffe & Josh Lerner, *Innovation and Its Discontents* (Princeton: Princeton University Press, 2004).

¹⁷¹ Sawicka and Bouchard, 2008; Bouchard 2009; 2010; Hemphill and Sampat 2011; Hemphill and Lemley 2011.

¹⁷² Korea-U.S. Free Trade Agreement [KorUS FTA], signed June 30, 2007. online: Office of the United States Trade Representative <<http://www.ustr.gov/trade-agreements/free-trade-agreements/korus-fta>>.

¹⁷³ After signing the KorUS FTA on 30 June 2007, the South Korean Government (SKG) prepared a scheme to implement the linkage provision. It includes a bill to amend the Pharmaceutical Affairs Act (PAA), and amendments of relevant Presidential Decree and Enforcement Regulations. The PAA amendment bill was published on October 2007 by the Legislative Bill Notice, but was not brought in to the National Assembly. While the PAA amendment bill mentions the general process, the amendments of the Presidential Decree and the Enforcement Regulations, which were not fully disclosed and outline of which has been made public twice by the KFDA at the public briefings in October 2007 and 2008, show the SKG's plan on the details of the linkage system. The PAA amendment bill was published on October 2007 by the Legislative Bill Notice and can be found at: Legislative Bill Notice No. 2007-331 of Minister of Public Health and

Welfare.http://www.mw.go.kr/front/jb/sjb0403vw.jsp?PAR_MENU_ID=03&MENU_ID=030403&BOARD_ID=200&BOARD_FLAG=00&CONT_SEQ=179172&page=1>. The South Korean Government (SKG) study can be found at:

http://www.mw.go.kr/front/al/sal0301vw.jsp?PAR_MENU_ID=04&MENU_ID=0403&BOARD_ID=140&BOARD_FLAG=00&CONT_SEQ=42437&page=1. A summary discussion and table from the study is found in Ministry of Health and Welfare. Analysis of Economic Impacts of the Korea-US FTA, April 27, 2007 and is available at http://www.google.co.kr/url?sa=t&source=web&cd=6&ved=0CDwQFjAF&url=http%3A%2F%2Fwww.mopas.go.kr%2Ffgpms%2Fresource%2Fimages%2Fkorea%2Fdown%2Ffta_070508_02.hwp&ei=9558TLu8FYPSsAOFrNGCBw&u sg=AFQjCNH7w7OnmGOAR53R00Ccw5I6x-X-bA&sig2=b08TQ94nGhjOpabTVOAXNw (pages 66-72). Finally, a specific discussion of pharmaceutical linkage regulations in the context of the KorUS FTA can be found at: Assembly Conference Records of the Committee of Health and Welfare, June 18, 2007, at 14-21.

¹⁷⁴ Production loss was estimated to be equivalent to 90.4B-168.8B KRW for the first ten years. Due to the production loss, about 369 to 689 persons would lose their jobs every year for the first ten years alone. The impact on consumer welfare (including the drug expenditure of the National Health Insurance and burden of patients) were estimated to be 39.7B KRW annually for the first ten years.

¹⁷⁵ EC Pharmaceutical Sector Preliminary Report; EC Pharmaceutical Sector Final Report.

¹⁷⁶ Faunce 2005.

Australia introduced both express anti-evergreening provisions (involving damages and penalties) as well as a provision for pharmaceutical innovation to be defined based on considerations of ‘objectively demonstrated therapeutic significance’ in its linkage regime, notwithstanding significant resistance from U.S. trade negotiators.¹⁷⁷ It remains to be seen whether this customized system of checks and balances will yield an empirically observable balance between the production of new and innovative drugs and timely generic entry.

A similar comparison can be drawn from the differing experiences of the United States, India, Australia, South Korea and Canada with regards to allegations of evergreening abuses. The U.S. FTC conducted a detailed arm’s length study of evergreening following allegations from numerous parties that abuses of the automatic stay led to undue monopoly protection and high drug prices in some instances.¹⁷⁸ The linkage regime was amended to curb certain abuses,¹⁷⁹ with evident success.¹⁸⁰ Canada, on the other hand, has not had the same level of public debate over drug pricing. In addition, the government has been slower to respond to evergreening allegations, and has minimized the negative effects of linkage on patent protection for blockbuster drugs in numerous internal studies released between 2004 and 2010.¹⁸¹ In India, the Supreme Court recently upheld the rejection by the High Court of Delhi of pharmaceutical linkage, and the nation clearly sees itself as a leader on the issues of global pharmaceutical law and access to essential medication. Evergreening abuses can be addressed in a unique way using traditional patent law: the nation’s patent law allows for filing of oppositions before the grant of a patent (pre-grant opposition) which allows competitors (mostly generics) to challenge the validity of a patent application before its grant.¹⁸² Indian companies have used pre-grant opposition to effectively challenge some of the most profitable drugs, including Glivec, Cialis, Iressa, Prezista, Nexium, Tamiflu, etc.

Why is Canada lagging behind the United States in its law reform efforts? Why is South Korea going forward even though its own data are projecting negative domestic impacts? Why have some jurisdictions such as Australia and India responded quickly and effectively to public interest concerns in bringing in, amending, and/or rejecting their domestic linkage regimes and what lessons are there for other jurisdictions? One possible obstacle to effective policy-making and/or law reform is that linkage regulations are complex and not widely understood. This is consistent with the observation in *Bayer v. India* to the effect that there is no uniformity in the linkage policy of different countries.¹⁸³ Hence, the value of a comparative legal analysis of different linkage systems worldwide.

A related and important issue is presented by the manner in which courts in different jurisdictions view the role of empirical data in the context of an evolving legal landscape,

¹⁷⁷ Faunce, 2005; Faunce & Lexchin, 2006.

¹⁷⁸ FTC Study 2002.

¹⁷⁹ Avery, 2008.

¹⁸⁰ Epstein & Kuhlik 2004; Avery 2008.

¹⁸¹ *Canada Gazette* (12 March 1998) Vol. 132, No. 7.; *Id. Canada Gazette* (1 October 1999) Vol. 133, No. 21. Evidence of legislative intent regarding the “original policy intent” of encouraging development of new and innovative drugs can be found in both RIAS and related Guidance Documents: *Canada Gazette* (11 December 2004) Vol. 138, No. 50; *Id.* (17 June 2006) Vol. 140, No. 24.; *Id.* (25 June 2008) Vol. 142, No. 13.; Health Canada Guidance Document. *Patented Medicines (Notice of Compliance) Regulations* (3 April 2009). An articulation of the government’s pharmaceutical policy as it relates to the NOC Regulations can be found in the 2006 RIAS, which states at 1510: “The Government’s pharmaceutical patent policy seeks to balance effective patent enforcement over new and innovative drugs with the timely market entry of their lower priced generic competitors. The current manner in which that balance is realized was established in 1993, with the enactment of Bill C-91, the Patent Act Amendment Act, 1992, S.C. 1993, c. 2.”

¹⁸² Khader, Feroz Ali, *The Touchstone Effect: The Impact of Pre-grant Opposition on Patents* (India: LexisNexis Butterworths, 2008).

¹⁸³ *Id.*, at para 32.

particularly with respect to technology-heavy areas of the law such as intellectual property.¹⁸⁴ A pertinent question that arises is how *should* courts and law-makers react when empirical evidence demonstrates that a particular piece of legislation is not achieving its stated goals? Can such data support the conclusion that the legislation is invalid or in need of substantial amendment in order for it to remain *intra vires*? Are there aspects of statutory interpretation in various jurisdictions that illuminate an investigation into whether the local linkage laws are meeting the stated goals of stimulating the development of new and innovative drugs and facilitating timely entry of generic drugs and if not what should be done about it? An ancillary question is whether appellate courts in different jurisdictions view law as “live” or “fixed” - and thus - more or less amenable to *ex post* empirical analysis.

Our work thus far suggests it may be particularly useful to investigate the *vires* of pharmaceutical linkage from a purposive perspective, using ordinary language of linkage statutes informed contextually by the scheme, purpose and evidence of statutory intent.¹⁸⁵ This approach supports an important role for external context, referring to the interface between original policy intent and the consequences of how legislation works operationally in the real world.¹⁸⁶ Taking an “evidence-based” approach to the assessment of *vires* in a technology-intensive sector such as pharmaceuticals resonates particularly well with the state of global drug regulation, which has clearly and strongly evolved toward “real world,” or evidence-based lifecycle, models of drug approval for the last two decades.¹⁸⁷

If drug approval and drug patenting are becoming increasingly evidence-based, there is no reason why the legal linkage between the two should do so as well. An evidence-based approach to *vires* is also supported by the objective in some statutory analysis cases of probing the mischief a given piece of legislation was intended to remedy at the time it was enacted.¹⁸⁸ In the case of linkage statutes or regulations, this exercise would likely be contingent both on an understanding of the original policy intent underpinning local linkage regimes as well as their enabling statutes, typically patent legislation.¹⁸⁹ When courts are presented with competing interpretations of law (e.g., public health or economic; patent law or food and drug law), is the clear choice one that accords substantively with a legislative purpose that is consistent with an interpretation of the statute as a workable whole?¹⁹⁰ As noted by Fuller:

“The troublesome cases are in reality resolved not in advance by the legislator, but at the point of application. ... All this adds up to the conclusion that an important part of the statute in question is not made by the legislator, but grows and develops as an implication of complex practices and attitudes which may themselves be in a state of development or change.”¹⁹¹

¹⁸⁴ Burk and Lemley 2002.

¹⁸⁵ Ruth Sullivan, *Sullivan and Driedger on the Construction of Statutes*, 4th ed. (Vancouver: Butterworths, 2002), at 7 and 20.

¹⁸⁶ Cameron Hutchinson, “Which Kraft Statutory Interpretation? A Supreme Court of Canada Trilogy on Intellectual Property Law” (2009) 46 Alta. L. Rev. 1.

¹⁸⁷ 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). For a discussion of the relevance of lifecycle models to pharmaceutical linkage, see: Bouchard and Sawicka 2008.

¹⁸⁸ Hutchinson 2009, at note 29, citing William N. Eskridge, Philip P. Frickey & Elizabeth Garrett, *Legislation and Statutory Interpretation*, 2nd ed. (New York: Foundation Press, 2006).

¹⁸⁹ Bouchard 2011.

¹⁹⁰ Lon L. Fuller, “Positivism and Fidelity to Law – A Reply to Professor Hart” (1958) 71 Harvard Law Review 630, at 667; Lon L. Fuller, *Anatomy of the Law* (New York: Frederick A. Praeger Publishers, 1968). For a discussion of Fuller’s work in the context of intellectual property litigation, see *supra* note 123.

¹⁹¹ Fuller, 1968 at 59. As noted by Hutchinson 2009 at note 32 and note 116: “The process of interpreting statute is not just

In this view, the purpose of law is not static but rather a dynamic process of refining and clarifying means and ends through a system of positive and negative feedback loops.¹⁹² The purposive analysis thus privileges evidence of *how* a law operates in the lives of people affected by it, not theoretically or hypothetically as an isolated idea or goal. In an analytical framework of this nature, objective evidence of the operation of statutes and regulations such as empirical evidence of contextual operational efficiency is paramount.¹⁹³

The notion that law is “alive” rather than stagnant draws strong parallels to legal scholarship demonstrating law to be a dynamic complex adaptive system.¹⁹⁴ In such systems, law-in-operation is strongly contingent on evidence relating to positive and negative feedback loops that impact on system performance, including empirical data relating to systems of intellectual property law and biomedical innovation.

G. Ghost Linkage

As discussed in Section IV.C. *supra* addressing the issue of policy convergence, different jurisdictions have taken substantially different courses on whether to combine health policy with industrial and economic policy, with the European Union and India firmly rejecting linkage based on the desire to retain functional separation between food and drug law and intellectual property law. Having said this, we note the possibility that jurisdictions without formal linkage measures may nonetheless permit practices by brand pharmaceutical firms within their existing intellectual property frameworks that can yield a system with functional characteristics that are similar to those where linkage is in place. One might refer to intellectual property systems of this nature as “ghost linkage,” as the spirit (or less metaphorically, the strategy) driving drug development even in the absence of a formal body of linkage laws remains that underpinning product clusters, or portfolio-based innovation.

The European Union recently conducted a wide-sweeping detailed investigation into empirically observable strategies and behaviors of brand and generic pharmaceutical firms in Europe (European Commission Pharmaceutical Sector Inquiry, or Commission). The report gives much cause for concern with regard to ghost linkage even though the Commission explicitly concluded that pharmaceutical linkage is contrary to the law of the European Union.¹⁹⁵ The implications of the report for cluster-based drug development arise not only arise at the level of infringement-based litigation between brand and generic firms, but spans a wide range of legal and regulatory activities relating to drug approval, patenting, pricing, promotion and reimbursement practices, cross-border movement of drugs and drug components between nations with varying degrees of TRIPS-compliance, and in relation to distribution channels and supply sources for ingredients needed to produce therapeutic products.

drawing out what legislator put into it but adjusting the statute to the implicit demands and values of the society to which it is to be applied. “In this sense it may be said that no enacted law ever comes from its legislator wholly and fully “made”.”

¹⁹² Hutchinson 2009, referring to Fuller 1958, at 668.

¹⁹³ Hutchinson 2009.

¹⁹⁴ John H. Miller & Scott E. Page, *Complex Adaptive Systems: An Introduction to Computational Models of Social Life* (2007).

¹⁹⁵ European Commission Pharmaceutical Sector Inquiry Final Report, 8 July 2009, at 23 [EC Pharmaceutical Sector Report]. This theme is developed extensively in the European Commission Pharmaceutical Sector Inquiry Preliminary Report, 28 November 2008 [EC Pharmaceutical Sector Preliminary Report], at pp. 14 and 113. At page 15 of the Preliminary Report, the Commission states that “Patent-linkage is considered unlawful under Regulation (EC) No 726/2004 and Directive (EC) No 2001/83.”

As a starting point, we note that the purpose of the network of laws underpinning the E.U. pharmaceutical system has policy goals which clearly parallel those underpinning formal linkage regimes. In its Final Report,¹⁹⁶ the Commission notes it is “committed to the promotion of innovation through industrial property rights, including patents” and that such promotion is in service of “high quality patents granted in efficient and affordable procedures and providing all stakeholders with the required legal certainty.” In the next paragraph, the Commission goes on to say: “At the same time, it is generally acknowledged that public budgets, including those dedicated to cover health expenditure, are under significant constraints. Competition, in particular competition provided by generic medicines, is essential to keep public budgets under control and to maintain widespread access to medicines to the benefit of consumers/patients.” The Commission underscored the point that generic medicines should reach the market without unnecessary or unjustified delay, and that to fully benefit from the cost savings brought about by generic products that its Member States would need to have in place policies that facilitate timely generic uptake in terms of both volume and price competition.

As observed by one commentator,¹⁹⁷ the Commission’s report is predicated on the assumption that patent protection favors competition because it encourages both investments into new and innovative products by brand firms while also encouraging the marketing of generics at lower prices. The costs savings from generics feeds back into the system, which in turn contributes to positive consumer welfare outcomes and creates incentives for further innovation.¹⁹⁸ Thus, the policy grounds for pharmaceutical law in the European Union are very similar to those in jurisdictions with linkage that explicitly speak of the need to balance the competing goals of stimulating the development of new and innovative drugs and facilitating timely generic entry.

Similar to the originating linkage regimes in the United States and Canada, the European Union recently introduced a Bolar provision, through Directive 2004/27/EC amending Directive 2001/83/EC regarding relevant code relating to medicinal products for human use.¹⁹⁹ As discussed above in Section IV.A., there is of course no reason why a Bolar, or early working, provision must per se lead to linkage systems allowing product evergreening. However, it is noteworthy that both originating linkage systems came into force based on Bolar-type amendments, and that E.U. law has recently provided for same amidst some backlash focusing on the need for enhanced patent rights for brand firms. This raises the question of whether the early working provision of Bolar would be “balanced” by linkage-style evergreening practices.

Indeed, the scope of the E.U. Bolar provision has been criticized, including by the Pharmaceutical Sector Inquiry,²⁰⁰ as ambiguous and uncertain in scope.²⁰¹ The basis for most

¹⁹⁶ Final Report, at 2.

¹⁹⁷ Shan Hu. European Commission issues report on pharmaceutical sector inquiry. 15 Colum. J. Eur. L. Online 27 (2009). <http://www.Cjel.Net/Online/15_2-Hu/>.

¹⁹⁸ Final report, at 29.

¹⁹⁹ This exception provides the manufacturers of generic medicines an exemption for pre-market testing: “Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.”

²⁰⁰ Final Report, at para 317.

critiques of the European Bolar provision is that inconsistent legal application across Member States yields a situation where the legal landscape regarding early-working and the experimental use exemption for research has significantly hindered the functioning of the E.U. market for pharmaceuticals, particularly with regards to timely generic entry. Concerns as to the scope of the Bolar provision led the European Generic Medicines Association to express concern that the provision will not only allow linkage of patent status to marketing authorization, but also to drug pricing and reimbursement schemes.²⁰² In its report, the Commission stated that the express objective of the Bolar provision is to “create a safe harbour for certain tests and studies while the reference product is still patent-protected so as to enable the generic producer to apply for marketing authorisation...”²⁰³

Despite the specificity of the Commission’s articulation regarding the scope of Bolar, interpretive discretion on the part of domestic governments has nevertheless led in practice to a patchwork quilt of differing provisions in differing E.U. states, with the result that different jurisdictions remain open to customization of domestic intellectual property laws such that a balance of early working and linkage can be introduced through Bolar amendments to domestic patent legislation. As a result, there remains a significant possibility that the Bolar provision may operate in the European Union as a vehicle to provide for multiple patent listings on multiple related products within a given product cluster.²⁰⁴ This would be particularly relevant in jurisdictions, such as Hungary, Italy, Portugal, the Slovak Republic etc., which have provided for some form of linkage in their domestic intellectual property law notwithstanding European Union law to the contrary.²⁰⁵

A third attribute of pharmaceutical law in the European Union that parallels linkage is the blocking function of interlocutory injunctions sought by brand firms. Exploratory infringement suits seeking as remedy interlocutory injunctions provides a similar function to the automatic stay, which as discussed in Section IV.B above, represents a fundamental feature of pharmaceutical linkage. When operating as a positive feedback loop - with success after the first injunction breeding further and faster success downstream in later proceedings - successful injunctions per drug or product cluster operate to effectively chill generic entry.²⁰⁶ A recent study of litigation in the European Union revealed that even where such disputes are few in number, they nevertheless have a strong negative effect on the entry of generic products as a result of the mere threat of costly litigation and risk of further interim injunctions. The data reported by the Commission showed that over half of proceedings against generics were preceded by prior disputes. The study concluded that the chilling effect

²⁰¹ Kristof Roox. The Bolar provision: A safe harbor in Europe for biosimilars. EURAkex, Issue 172. 19-20. 2006; Sean O’Connor. Enabling research of unfair competition? De jure and de facto research use exemptions in major technology countries. In *Comparative Patent Law: A Handbook of Contemporary Research*. Takenak et al. eds. (Edward Elgar, 2008).

²⁰² EGMA. Patent-related Barriers to Market Entry for Generic Medicines in the European Union, at 23.

²⁰³ Preliminary, at 260.

²⁰⁴ At 260 of Preliminary Report: This provision, which was introduced by Directive 2004/27, creates a safe harbour for certain tests and studies while the reference product is still patent-protected so as to enable the generic producer to apply for marketing authorisation once the eight-year period of data exclusivity granted to the holder of the original MA has elapsed.

²⁰⁵ Prelim, at para 716 and Table 22.

²⁰⁶ Caffrey and Rotter; 2003; Hore 2004.

of even a small number of proceedings “illustrates the strength of the link between patent-related exchanges and patent litigation.”²⁰⁷

Brand firms requested interim injunctions in 225 cases studied by the Commission between 2000 and 2007.²⁰⁸ Firms were successful in a remarkable 112 of these cases, or 48% of the time. The average duration of interim injunctions in this test group was 18 months. Importantly, in almost half (46%) of the cases in which injunctions were granted to brand firms, subsequent court proceedings ended either with final judgments favorable to the generic company or settlements which favorable to the generic company. Interim injunctions were granted, on average, for a period of 18 months. A significant proportion of injunctions (46%) were granted for a period exceeding one year, with 30% of injunctions granted for a period lasting between 1 and 2 years and 16% for a period exceeding 2 years.²⁰⁹ In the context of questioning whether or not harmonized E.U. laws on topic might be preferable, the Commission stated that “there are considerable differences between the courts in different Member States in the ease or reluctance with which they grant interim measures. Depending on national law, a generic company may also take the initiative itself to ask for a declaratory ruling of non-infringement prior to launching a generic product, or launch a revocation proceeding before the court.”²¹⁰ Thus, as with formal linkage regimes, the interim injunction has been used to effectively delay generic entry under the law of the European Union. It appears that it is reasonable to posit that, in the absence of harmonized regional or global laws on point, brand firms will game the system effectively in service of “lifecycle-based” drug development strategies.

One of the greatest concerns in jurisdiction with formal linkage regimes is the combination of a weak relevance requirement for patent listing and the grant of weak patents, as together they combine to delay generic entry on patents that are potentially invalid or not infringed by generic substitutes. This was the topic of discussion in the content of linkage in Section IV.A., *supra*. Therefore, it is with interest that we note that as with litigation under linkage in the U.S. and Canada,²¹¹ the majority of brand claims as to validity or infringement in litigation between brand and generic firms were unsustainable on review by the court.²¹² Data reported in the Preliminary Report illustrated that generic firms won the majority of all patent litigations reported in which a final judgment was delivered (62%), whereas brand firms were successful in considerably fewer cases (38%). When initiated by generic firms, in litigation that can be seen to be analogous to the Notice of Allegation which begins proceedings under North American linkage, generic companies won nearly three quarters of all patent cases (71%).²¹³ By comparison, brand firms were successful in slightly over half of the cases they initiated (51%).²¹⁴ Not dissimilar to early data on linkage in the U.S.²¹⁵ and Canada,²¹⁶ cumulative data indicated that generic companies won in excess of 60% of all patent litigation initiated in the European Union over the 2000 to 2007 test period. As noted

²⁰⁷ European Commission Pharmaceutical Sector Inquiry Preliminary Report 2008, at para 458 (p. 174).

²⁰⁸ Fact Sheet, at 3.

²⁰⁹ Prelim, at 525.

²¹⁰ Final Report, at para 283.

²¹¹ FTC 2002; Hore 2004.

²¹² Prelim Report. See e.g., Fig. 118.

²¹³ Prelim, at 508.

²¹⁴ Prelim, at 504-505.

²¹⁵ FTC 2002.

²¹⁶ Hore 2004

by the Commission, this outcome was achieved at the expense of repetitive, lengthy and costly litigation before different national jurisdictions, with the result of increased costs to consumers and increased financial and legal uncertainty for generic firms.²¹⁷

Of relevance to the product cluster theory of drug development, generic companies won nearly 75% of all cases concerning secondary patents on follow-on drugs. By contrast, brand firms were successful in slightly greater than one quarter of litigations over such patents.²¹⁸ As noted by the Commission,²¹⁹ this litigation leads to a substantial delay of generic entry and increased costs to system. Regarding cost estimates passed on to consumers, brand firms were estimated to pay on average €230,000 in legal fees per case in single Member States, with a high of €993,000 per litigation in the United Kingdom. The total cost of patent litigation in the E.U. over the test period was expected to exceed €420 million.

While litigation pursuant to listing patents on a patent register does not take place in the European Union, there is a parallel pathway for challenging generic entry linked to patent status referred to as an “intervention.” This term refers to third party intervening (by brand firms) before national authorities deciding on marketing authorisation, pricing and reimbursement of generic products. The growing number and scope of linkage-related interventions before regulatory authorities suggests that even if the system of food and drug law in the European Union does not formally admit linkage it may in practice allow parallel actions by brand firms that have similar *outcomes* to those in jurisdictions with linkage.

Interventions included submissions before national authorities in regards to generic marketing authorisation, pricing, and reimbursement status. In particular, brand firms claimed that generic substitutes were less safe, less effective and of inferior quality than brand comparator products, claiming that marketing authorisations, pricing, and reimbursement status violate brand patent rights.²²⁰ The Commission observed that when a brand firm intervened in marketing authorization decisions, marketing authorisation took, on average, four months longer, with substantially delayed market entry on “blockbuster” drugs. The Commission noted that “According to their internal documents, originator companies themselves believe that significant additional revenues result from such practices.” It is clear from both the volume and scope of interventions that brand firms are lobbying regulators for outcomes similar to those they are obtaining in jurisdictions with formal linkage regimes. The degree to which brand firms will be successful in the future will depend on the understanding of E.U. Member States regarding the parallels between the two intellectual property systems used to protect and encourage the development of new and innovative pharmaceuticals while also encouraging the timely entry of generic substitutes.

Finally, some discussion of the product cluster, or portfolio-based, drug development strategy is relevant in the European Union context. This is so because this approach seems to be so strongly supported by the system of checks and balances inherent to linkage regulations and it is somewhat unclear whether the same approach can be supported by more “traditional” patent systems. Indeed, based on the findings of the Commission, it is

²¹⁷ Prelim at 505.

²¹⁸ Prelim, at 508.

²¹⁹ Prelim, at 531-533.

²²⁰ Fact Sheet, at 4.

reasonably clear that the portfolio-based approach to innovation is alive and well in the European Union despite the lack of linkage laws.²²¹ As stated by the Commission:

“One common strategy is the creation of “patent clusters” by the filing of numerous additional patents for the same medicine. The following quotes, found in documents collected in the inspections of originator companies, confirm that one of the objectives of this strategy is to delay or block the market entry of generic medicines.”²²²

The report, citing two such quotes, continued:

The strategy today is to try and provide a solid protection for the substance (has a limited time though) and a portfolio protecting different aspects of product providing extended protection both in breadth and time but inevitable less solid and robust.²²³

Before end 80s: Products mainly NCEs which were protected by the one patent- [...] Late 80s – early 90s[...] Expansion of the portfolio to cover lifecycle initiatives, to extend protection time for product and the breadth of the protection trying to keep competition further away.”²²⁴

Using a strategy well known to those familiar with linkage laws, brand firms in the European Union have been reported to frequently attempt to transition patients using brand products facing imminent loss of exclusivity to follow-on products from the same company. The Commission found that brand firms launched such follow-on drugs in relation to 40% of the medicines in the sample selected for investigation which had lost exclusivity between 2000 and 2007.²²⁵ This is wholly consistent with the empirical find that brand firms operating in the North American context of linkage have been very successful at obtaining approvals, patents, and listing such patents on the patent register, with the specific intent of delaying generic entry.²²⁶ As noted by the Commission, the launch of follow-on drugs is accompanied by intensive marketing efforts designed to convert patients to follow-on drugs before generic entry,²²⁷ with the result that both generic entry as well as generic market share once entry is accomplished is delayed and reduced.²²⁸ It would not be unreasonable to speculate that the timing of cluster-based drug development by multinational pharmaceutical firms coincides with the coming into force of the first linkage regimes – first, the Hatch Waxman regime in the United States and then second, the NOC Regulations in Canada - following which multinational firms expanded linkage-based drug development strategies globally.

Regarding patents relating to product clusters, the Commission noted that brand firms file an onerous number of patent applications in order to create patent clusters around one product, and that the result of this strategy is an increase in the number of weak patents.²²⁹ An increase in weak patents is supported by the finding of the Commission that in patent

²²¹ For a full discussion of patent clusters, see the discussion in the Final Report, at para 470-506, especially Figs 59-60. See also paras 20, 167 and 446 of the Final Report, the Prelim Report, at paras 376-397, and, pages 5, 9-10.

²²² Fact Sheet, at page 1.

²²³ Fact Sheet, at page 1.

²²⁴ Final Report, at para 383.

²²⁵ Fact Sheet, at 4-5.. See final Report, at 297.

²²⁶ Sawicka and Bouchard, 2008; Bouchard 209; Bouchard 2010.

²²⁷ Final Report, at 305-306.

²²⁸ Final Report, at 310.

²²⁹ Prelim Report, at para 393.

litigation between brand and generic firms the majority of litigated patents were revoked. Not surprisingly, the picture is bleaker when follow-on patents are assessed, where generic firms won nearly three quarters (74%) of all cases concerning secondary patents in which a final judgment was levied. By contrast, brand firms won only one quarter of cases over follow-on patents (26%).²³⁰ The Commission found that generic firms won the vast majority of litigation over second medical use patents (83%), and had equal success challenging first medical use patents, with final judgments favoring generics in “the overwhelming majority of litigations (88% of all cases) compared to only 12% in favor of the originator party.”²³¹ These are important findings for jurisdictions with and without formal linkage regimes, as the data speak to the validity of the social value of a *regulatory preference* (based either on linkage or traditional patent law) for follow-on innovation and drug development strategies.

The product cluster approach is also the focal point of the Commission’s assessment of the content and value of the “toolkit” of drug strategies employed by brand firms in order to delay generic entry using loopholes in E.U. drug law and regulations. The Commission found that brand firms “use a variety of strategies and instruments to maintain revenue streams from their medicines, in particular blockbusters, for as long as possible.”²³² These practices can delay generic entry and lead to healthcare systems and consumers paying more than they would otherwise have done for medicines.” The strategies identified by the Commission, familiar to those working with the U.S. Hatch Waxman, Canadian NOC Regulations, and newer linkage regimes, include: (1) strategic patenting, (2) patent disputes and litigation, (3) patent settlements, (4) interventions before national regulatory authorities, and (5) lifecycle strategies for follow-on products.²³³

While it was noted that the intended effects of patent clusters to delay generic entry is “generally in line with the underlying objectives of patent systems,” the strategy nevertheless appears to be aimed exclusively at “excluding competition and not at safeguarding a viable commercial development of own innovation covered by the clusters.”²³⁴ The Commission elaborated later in its report, stating that the “denser the web created by patent clusters the more difficult it is for generic firms to bring its generic version to market.” The strategy for the extension of exclusivity in the context of patent clusters was seen to be “... even though the main patent protecting the product, e.g. the basic substance patent, may have expired, the generic version may still infringe one of the multiple patents surrounding the original pharmaceutical. This can occur either because patents cover all economically interesting or viable salt forms, enantiomers or formulations of the compound or all efficient ways of its manufacturing.”²³⁵

In the concluding words of the Final Report, the Commission confirmed system outcomes that are almost identical to those described in Sections IV.A-F. *supra* for formal pharmaceutical linkage; that is, delayed generic entry and a decline in the production of novel medicines. Thus, it is fair to say that in both systems of intellectual property law that the same policy goals not being met for the same, or at least substantially similar, reasons. The

²³⁰ Prelim, at para 508.

²³¹ Prelim, at para 512-513.

²³² Fact Sheet, at 1.

²³³ *Id.*, at 1.

²³⁴ Prelim, at para 410.

²³⁵ Prelim, at para 412.

Commission concluded by saying that the same company practices that dominate jurisdictions with well-established linkage regimes are the cause of these outcomes. The solution, apparently, lies in more market monitoring²³⁶ and continued dialogue with all stakeholders to ensure that the innovative potential of the pharmaceutical industry can fully develop and that the public has access to safe and innovative medicines at affordable prices without undue delay.²³⁷ No mention is made of closing loopholes in legislation or regulations that permit product cluster-based drug development and portfolio-based innovation strategies to be successfully leveraged.

Based on this brief review of the empirical observations made by the Commission, it will be important for jurisdictions without formal linkage regimes to appropriately monitor the interplay of different policy levers in so far as they have the capacity to interact together to parallel drug development and innovation outcomes observed under linkage.

V. SUMMARY & CONCLUSIONS

Compared to the traditional patent system, pharmaceutical linkage regulations represent a novel and evolving intellectual property paradigm for pharmaceutical products. Even so, this regime is rapidly evolving in a global context, and is poised to become an increasingly important determinant of the availability and cost of essential medications worldwide. In this Article, the authors, representing a network of scholars and practicing lawyers, lay out a framework for a comparative legal analysis of global pharmaceutical regulations.

A major goal we have identified is to investigate the structural and functional aspects of global linkage regulations as they relate to drug availability, costs and expenditures on the one hand and incentives for innovation and protection of rights on the other. A unique advantage of the structure-function methodology proposed in this Article is that studying linkage in different jurisdictions in this manner allows for both: an investigation of the structural and functional characteristics of local linkage regimes with different initial starting conditions and different legal mechanisms of operation; and the identification of general rules of linkage as the different national forms of linkage interact and influence global pharmaceutical regulation. The former provides a *descriptive* mechanism for assessing the successes and failures of different regimes while the latter provides a *prescriptive* approach for key decision makers to revise, institute or abolish linkage regulations according to the goals and objectives of differing nations.

The structural and functional aspects we discuss in this article include: assessment in each jurisdiction of the original policy intent underpinning linkage; the specific legal grounds underpinning linkage in various jurisdictions, in particular the Bolar provision and how this provision interacts with other policy levers intended to stimulate innovation while also making generic drugs available faster; the manner in which public health policy and economic policy is perceived by governments and the courts to converge or diverge through linkage; the specific legal checks and balances designed specifically to maintain balance between the interests of brand and generic firms; the growing expansion of linkage beyond the drug approval-drug patenting nexus to encompass drug pricing and reimbursement; and the role of empirical studies to establish the legal legitimacy of linkage regulations.

²³⁶ Final Report, at para 1607.

²³⁷ Final Report, at para 1612.

The goal of the work outlined here is to assist key decision-makers and knowledge users in domestic and global governments and legal systems working with linkage regimes in their efforts to stimulate the production of new and innovative drugs while at the same time facilitating timely generic entry, lowering public health costs, and increasing access to essential medicines.

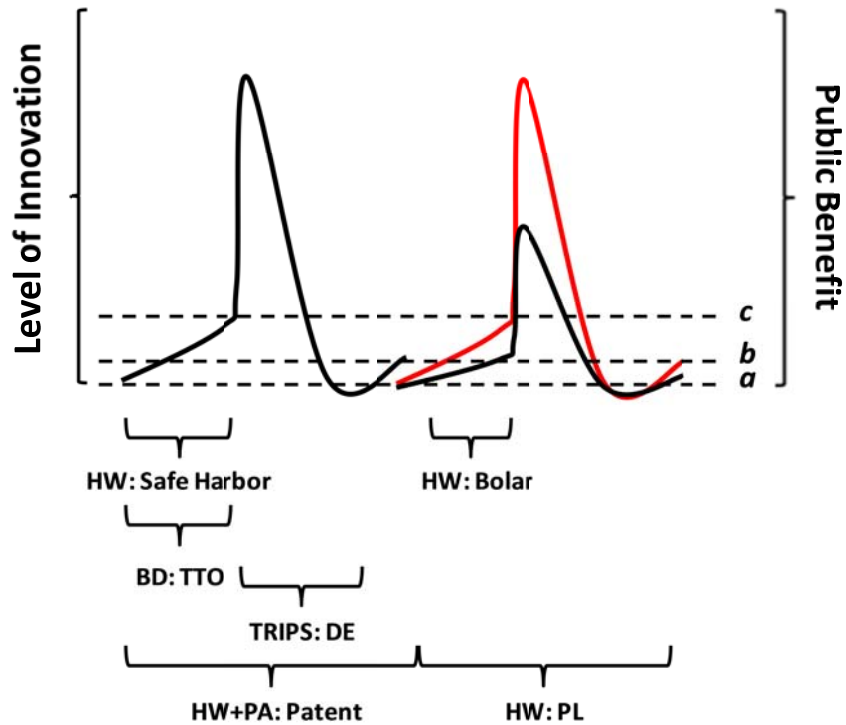


Fig. 1. Therapeutic Product Lifecycle Innovation Incentives. The figure illustrates the complex interrelated legal mechanisms comprising the system of innovation incentives for brand and generic drug development. The left and right y axes are qualitative innovation and public benefit indices. The x axis represents the product development lifecycle over time. Black waveforms represent the progression of drug development from publicly funded university research to commercialization of medical products by firms (large peak), followed by subsequent genericization (smaller peak). The slow ramp to peak in each case represents the amount of research and development necessary to prepare for and obtain regulatory approval. As indicated by the dotted black lines, the degree of innovative research involved in going from baseline (*a*) to brand products (*c*) is much greater than that required for generic drugs (*b*). The red waveform normalizes the generic curve for public benefit owing to price competition. Brand and generic drug development are incented at various points in the lifecycle by numerous policy levers, including the broad (research and development) and narrow (Bolar) components of the Hatch Waxman (Title I) safe harbor provision, patenting by universities and firms stimulated by Bay-Dole and the traditional patent system, patent term extension under Hatch Waxman (Title II), data exclusivity for brand regulatory submission packages under TRIPS and other FTAs, and pharmaceutical linkage under Title I of Hatch Waxman. Time gates for the various policy levers illustrated at the bottom of the figure are not intended to be closed, but rather reflect their general timing in the context of the product development lifecycle.