# ARTICLE

# QUALIFYING INTELLECTUAL PROPERTY I: HARMONIZED MEASUREMENT OF NEW AND FOLLOW-ON DRUG APPROVALS, PATENTS AND CHEMICAL COMPONENTS

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#### ABSTRACT

The purpose of this study was to develop a harmonized method to collect, compare and quantify regulatory approval, patenting and chemical data from multiple cohorts of new and follow-on drugs. The range of drugs studied encompassed all drug classes enumerated, described and prioritized by drug regulators in developed nations, with a specific focus on Canada. A related purpose was to address uncertainty in the pharmaceutical innovation literature regarding approval nomenclature, such as whether certain drugs should be called new or follow-on, follow-on or Me Too, and whether the Me Too and First in Class designations refer only to drugs approved via the new drug approval route or should also refer to drugs that are line extensions. In total, 2,087 drug approvals, 5,011 patents and 130 chemical components were analyzed. Drugs approved via new drug, line extension (or "supplemental"), and generic approval routes were studied. The first major observation was that the greatest fraction of all approval, patenting and chemical indicators were associated with line extension drugs generally and line extension Me Too drugs in particular. Conversely, the smallest fraction of all three indicators observed was in relation to the most innovative drugs class identified. The second trend is in relation to drugs in classes other than the Me Too class. As one moved from approvals, to patenting, to chemical components, an increasing fraction of all indicators studied, particularly for the most profitable drugs, was associated with drug products going through some form of expedited review or drugs containing a new active substance (also referred to as a new chemical entity). Thus, while brand firms are putting most of their effort into developing line extension and Me Too drugs, therapeutic products moving through expedited review and drugs with a new active substance designation are also attracting significant drug development activity. Third, the percentage of most innovative approvals, patents and chemicals was limited for each indicator by the comparatively lower number of drugs that were First in Class, especially in the new drug category. This result suggests that a focus on new drugs that are First in Class would be an efficient way for brand firms to increase the level of innovation in their pipelines. The same conclusion applies to government incentives for drug development, including both patent and regulatory rights incentives. Fourth, the level of innovation increased steadily as one moved from drug approvals to drug patents and chemical components. This result suggests that the rank order of functional utility of indicators studied is chemicals > patents > approvals. Having said this, only approvals and patents demarcate the boundaries of legal protection for pharmaceuticals. A surprisingly large number of generic approvals, patents and chemical indicators was observed across cohorts. This result suggests that generic firms

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are accruing greater number of approvals, patents and chemical components than may have been previously recognized. The data also support the conclusion that generic firms are following the lead of their sister brand firms by creating clusters of related products and patents. A final consideration was to provide data for the qualitative innovation index for pharmaceutical patents and products described in the companion paper.

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#### I. TERMS & ABBREVIATIONS

Abbreviated New Drug Submission
NDS or SNDS drug
Total Approval, MP Approval, MP Patent or MP
Chemical data
Expedited Review
First in Class
SNDS or Generic drug
ANDS or SANDS drug
Approvals, patents and chemicals

Me Too	Me Too drug
MP	Most Profitable cohort for test period
NAS	New Active Substance
NCE	New Chemical Entity
New Drug	NDS drug
NDS	New Drug Submission
NDS NAS	NDS drug containing a NAS
NDS ER	NDS drug undergoing ER
NDS FIC	FIC drug approved via NDS route
NDS Me Too	Me Too drug approved via NDS route
NDS MI	Most Innovative New Drug
NOC	Notice of Compliance
NOC/c	Notice of Compliance with Conditions
PR	Priority Review
SANDS	Supplemental Abbreviated New Drug Submission
SNDS	Supplemental New Drug Submission
SNDS ER	SNDS drug undergoing ER
SNDS FIC	FIC drug approved via SNDS route
SNDS Me Too	Me Too drug approved via SNDS route
Total Approval	Cohort of total approvals for test period

#### II. INTRODUCTION

Governments around the world are increasingly engaged with the political mandate of innovation. It is a race no one wants to lose. Yet, despite the non-rival nature of knowledge, it is one few will win. Innovation is a fundamental gateway to national and global productivity and prosperity.<sup>1</sup> Nowhere is this truer than in the fields of science and technology, particularly the life sciences.<sup>2</sup> To date innovation is measured primarily using quantitative

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

<sup>&</sup>lt;sup>2</sup> See, e.g., EUROPEAN MEDS. AGENCY, THE EUROPEAN MEDICINES AGENCY ROAD MAP TO 2010: PREPARING THE GROUND FOR THE FUTURE, at 9-10, EMEA/H/34163/03/Final (2005) [hereinafter EMEA ROAD MAP]; U.S. DEP'T. OF HEALTH & HUMAN SERVS. & FOOD & DRUG ADMIN., INNOVATION OR STAGNATION: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS, at i, i (2004) [hereinafter INNOVATION OR STAGNATION];

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methods, with patents typically used as the major indicator of innovation.<sup>3</sup> Methods most often reported include counting patents, patent citations, prior art citations and related litigation outcomes.<sup>4</sup> Indeed, much of what governments and economic actors supporting innovation understand about the relationship between invention and innovation is currently shaped by measurements of patenting activity.<sup>5</sup> For example, patenting licensing, litigation and prior art citation data have provided useful indicators of general knowledge flows within and between different industries.<sup>6</sup> In addition, these metrics have helped to shape priority areas for government investment,

<sup>4</sup> The data include patent counts, assignee counts, number of forward citations, and average regulatory review time per patent. *See, e.g.*, Aaron S. Kesselheim & Jerry Avorn, *Using Patent Data to Assess the Value of Pharmaceutical Innovation*, 37 J. L. MED & ETHICS 176, 176-77 (2009); Mark A. Lemley, *Rational Ignorance at the Patent Office*, 95 NW. U. L. REV. 1495, 1497-98 (2001); Gideon Parchomovsky & R. Polk Wagner, *Patent Portfolios*, 154 U. PENN. L. REV. 1, 18-23 (2006).

<sup>5</sup> See, e.g., EXPERT PANEL ON COMMERCIALIZATION, *supra* note 1; GUTHRIE & MUNN-VENN, *supra* note 1. For an analogous discussion of the importance of industrial intellectual property incentives in national productivity and prosperity in the United States, see generally COUNCIL ON COMPETITIVENESS, *supra* note 1. See also: Robert Pithkethly. *The Valuation of Patents: A Review of Patent Valuation Methods with Consideration of Option Based Methods and the Potential for Further Research*. Background Paper for Discussion, United National – Economic and Social Council (21 August 2002) OPA/CONF.1/2002/6; Meir Perez Pugatch. *What is the Value of Your Patent? Theory, Myth and Reality*. Intellectual Property Frontiers: Expanding the Borders of Discussion. Stockholm Network Working paper. 14-17.

<sup>6</sup> Manuel Trajtenberg, A Penny for your Quotes: Patent Citations and the Value of Innovations, 21 RAND J ECON. 172, 172 (1990); Rebecca Henderson et al., Universities as a Source Of Commercial Technology: A Detailed Analysis of University Patenting, 1965-1988, 80 REV. ECON. & STAT. 119, 199 (1998); David C. Mowrey et al., Learning to Patent: Institutional Experience, Learning and the Characteristics of University Patents after Bayh-Dole, 1980-1994, 48 MGMT SCI. 73, 73-74 (2002); Jean O. Lanjouw & Mark Schankerman, Patent Quality and Research Productivity: Measuring Innovation with Multiple Indicators. 114 ECON. J. 441, 441 (2004).

Alan Bernstein, Toward Effective Canadian Public-Private Partnerships in Health Research, 168 CAN. MED. ASS'N J. 288, 288 (2003); 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, 823-824 (2008); Elias Zerhouni, The NIH Roadmap, 302 SCI. 63, 63 (2003).

<sup>&</sup>lt;sup>3</sup> For review of many empirical studies see generally JAMES BESSEN & MICHAEL J. MEURER, PATENT FAILURE: HOW JUDGES, BUREAUCRATS, AND LAWYERS PUT INNOVATORS AT RISK 75 (2008) and MICHELE BOLDRIN & DAVID K. LEVINE, AGAINST INTELLECTUAL MONOPOLY (2008).

including a focus on translational research in the medical sciences.<sup>7</sup> However, as discussed in detail in the companion paper,<sup>8</sup> a primary focus on either quantifying or qualifying intellectual property generally and patents in particular is acknowledged to be problematic. Therefore, while a rational model that is both evidence-based and expertise-based to value intellectual property is widely considered to be desirable, such a method has not yet been elucidated.

The need for a qualitative intellectual property framework is particularly important in the pharmaceutical industry. This is because drug products have become an essential element of domestic and global public health systems despite the fact that a range of concerns have been voiced regarding the willingness of the public to underwrite the cost of drugs that are extensions of already marketed products.<sup>9</sup> The debate over the social value of pharmaceuticals is usually framed in one of two contexts. The first is in relation to the value of patented medicines that are new drug products versus products referred to variously as follow-on, incremental, line extension, me too, and supplemental. Indeed, a wide range of critics has questioned the social value of follow-on innovations,<sup>10</sup> while others assert that follow-on drugs are a critical component of pharmaceutical innovation.<sup>11</sup> The issue consumes a

<sup>11</sup> See, e.g., Ernst R. Berndt et al., *The Impact of Incremental Innovation in Biopharmaceuticals: Drug Utilisation in Original and Supplemental Indications*, 24 (Suppl. 2) PHARMACOECONOMICS 69, 69, 71 (Supp. 2 2006); Joshua Cohen & Kenneth Kaitin,

<sup>&</sup>lt;sup>7</sup> See, e.g., EMEA ROAD MAP; supra note 2; INNOVATION OR STAGNATION, supra note 2; Bernstein, supra note 2; Eichler et al., supra note 2; Zerhouni, supra note 2.

<sup>&</sup>lt;sup>8</sup> Ron A. Bouchard, *Qualifying Intellectual Property II: A Novel Innovation Index for Pharmaceutical Products.* 29 SANTA CLARA COMP. & HIGH TECH. L. J. 1-112 (2012). [hereinafter QIP II Companion Paper].

<sup>&</sup>lt;sup>9</sup> Ron A. Bouchard et al., *The* Pas de Deux *of Pharmaceutical Regulation and Innovation: Who's Leading Whom?*, 24 BERKELEY TECH. L.J. 1461, 1465-66 (2009) [hereinafter Bouchard 2009].

<sup>&</sup>lt;sup>10</sup> See, e.g., MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT 74-76 (2004); JERRY AVORN, POWERFUL MEDICINES: THE BENEFITS, RISKS, AND COSTS OF PRESCRIPTION DRUGS (2004); MERRILL GOOZNER, THE \$800 MILLION PILL: THE TRUTH ABOUT THE COST OF NEW DRUGS 8-10 (2004); JAMES LOVE, CONSUMER PROJECT ON TECHNOLOGY, EVIDENCE REGARDING RESEARCH AND DEVELOPMENT INVESTMENTS IN INNOVATIVE AND NON-INNOVATIVE MEDICINES 20 (2003); Joel Lexchin, Intellectual Property Rights and the Canadian Pharmaceutical Marketplace: Where Do We Go From Here?, 35 INT'L J. HEALTH SERV. 237, 243 (2005); Drugs in 2001: A Number of Ruses Unveiled, 11 PRESCRIRE INT'L 58, 58 (2002) [hereinafter Drugs in 2001]; Aidan Hollis, Comment on "The Economics of Follow-On Drug Research and Development: Trends in Entry Rates and the Timing of Development," 23 PHARMACOECONOMICS 1187 (2005).

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significant amount of the time and resources of regulators, who are tasked with determining the procedures, priorities, and evidentiary standards for approving the many classes of new and follow-on drugs.<sup>12</sup> The second component of the debate over the social value of pharmaceuticals is in regard to the ability of brand-name drug companies to forestall generic entry on older blockbuster drugs under pharmaceutical linkage laws using so-called weak or defensive patenting strategies and practices. While it is now understood that both brand and generic firms play the system for their own ends,<sup>13</sup> support of generic firms has taken on a life of its own due to the presumed cost savings aspect of generic substitutes.<sup>14</sup> In fact, cost savings of generic drugs to the public and

<sup>12</sup> For review and references of the standards and procedures of approval in the United States, European Union and Canada, see Ron A. Bouchard & Monika Sawicka, *The Mud and the Blood and the Beer: Canada's Progressive Licensing Framework for Drug Approval*, 3 MCGILL J. L. & HEALTH 49, 53-63 (2009); Trudo Lemmens & Ron A. Bouchard, *Regulation of Pharmaceuticals in Canada*, CANADIAN HEALTH L. AND POL'Y 311 (3d ed. 2007).

Follow-On Drugs and Indications: The Importance of Incremental Innovation to Medical Practice, 15 AM. J. THERAPEUTICS 89, 91 (2008); Joseph A. DiMasi, Price Trends for Prescription Pharmaceuticals: 1995–1999, (2000) http://aspe.hhs.gov/health/reports/Drugpapers/dimassi-final.htm; Joseph A. DiMasi & Laura B. Faden, Competitiveness in Follow-on Drug R&D: A Race or Imitation?, 10 NATURE. REV. DRUG. DISC. 23 (2011); Thomas H. Lee, "Me-too" products – friend or foe?, 350 N. ENG. J. MED. 211 (2004); Joseph A. DiMasi & Cherie Paquette, The Economics of Follow-on Drug Research and Development Trends in Entry Rates and the Timing of Development, 22 PHARMACOECONOMICS 1, 1-2 (Suppl. 2 2004); Z. John Lu & William S. Comanor, Strategic Pricing of New Pharmaceuticals, 80 REV. ECON. & STAT. 108, 117 (1998); Albert Werthheimer et al., Too Many Drugs? The Clinical and Economic Value of Incremental Innovations, 14 INVESTING IN HEALTH: THE SOCIAL AND ECONOMIC BENEFITS OF HEALTH CARE INNOVATION 77, 77-79 (2001).

<sup>&</sup>lt;sup>13</sup> Andrew A. Caffrey, III & Jonathan M. Rotter, *Consumer Protection, Patents and Procedure: Generic Drug Market Entry and the Need to Reform the Hatch-Waxman Act*, 9 VA. J.L. & TECH. 1 (2004); Jeremy Bulow, *The Gaming of Pharmaceutical Patents, in 4* INNOVATION POL'Y AND THE ECONOMY: NAT'L BUREAU OF ECON. RES. (2004); Mathew Avery, *Continuing Abuse of the Hatch-Waxman Act by Pharmaceutical Patent Holders and the Failure of the 2003 Amendments,* 60 HASTINGS L.J. 171 (2008–2009); EDWARD HORE, PATENTLY ABSURD: EVERGREENING OF PHARMACEUTICAL PATENT PROTECTION UNDER THE PATENTED MEDICINES (NOTICE OF COMPLIANCE) REGULATIONS OF CANADA'S PATENT ACT (2004), http://www.canadiangenerics.ca/en/news/docs/patently\_absurd\_04.pdf.

<sup>&</sup>lt;sup>14</sup> Ron A. Bouchard et al., *Empirical Analysis of Drug Approval – Drug Patenting Linkage for High Value Pharmaceuticals*, 8 Nw. J. TECH. & INT. PROP. 174, 181-83 (2010) [hereinafter Bouchard 2010]; Ron A. Bouchard et al., *Structure-Function Analysis of Global Pharmaceutical Linkage Regulations*, 12 MINN. J. L. SCI. & TECH. 1, 391-92 (2011) [hereinafter Bouchard 2011].

other institutional payers explicitly formed one of the two policy goals for bringing in pharmaceutical linkage in originating jurisdictions.<sup>15</sup> This balancing of public and private interests in drug regulation is further reflected in the terms of the traditional patent bargain,<sup>16</sup> which is noteworthy as the goals and purposes of pharmaceutical linkage are said to be contingent on the first principals of patent law.<sup>17</sup>

A number of questions arise with respect to the social value of brand-name and generic pharmaceuticals as framed above. Regarding brand drugs, the differential outcomes of regulatory and economic incentives for developing various classes of new and follow-on drugs is unclear in part due to a lack of understanding of the discrete nomenclature used by regulators for various drug classes, the different evidentiary requirements for approval of these drugs, and how different types of drugs can be used to extend the life of older blockbuster drugs about to come off patent. For example, is a drug with the same biological mechanism of action and indication as an already marketed drug considered a First in Class or Me Too drug? Are Me Too and First in Class drugs properly considered "new" or "follow-on" drugs? What exactly is meant by the term "line extension"? Are all line extension drugs of low innovative value as some have claimed or do some types of line extensions have more value than previously thought? What type of drug constitutes a true breakthrough drug or a "new and innovative" drug? How might a regulatory preference for one class of drugs affect other classes of new and follow-on drug development?

Other questions arise with regard to the relationship between the different classes of drug approvals, the patents associated with these drugs, and the ability of such patents to incent pioneering drug development and forestall generic entry. For example, what is the patenting activity associated with various classes of new and follow-on drugs, and why might different patterns of drug patenting matter to the public and public policy said to underpin pharmaceutical innovation? What type of drug development is being incented by the current basket of intellectual property and regulatory rights? How, if at all, do patents protect new and follow-on drugs differently, and how are

<sup>&</sup>lt;sup>15</sup> Bouchard 2011, *supra* note 14, at 437.

 $<sup>^{16}</sup>$  E.g., Graham v. John Deere Co., 383 U.S. 1, 8 (1966); KSR Int'l v. Teleflex, Inc., 550 U.S. 398, 419 (2007); Farbwerke Hoechst Aktiengesellschaft Vormals Meister Lucius & Bruning v. Comm'r of Patents [1966] S.C.R. 604, 617 (Can.); Whirlpool Corp. v. Camco, Inc., [2000] 2 S.C.R. 1067, J 37 (Can.); Free World Trust v. Électro Santé Inc., [2000] 2 S.C.R. 1024, J 13 (Can.).

<sup>&</sup>lt;sup>17</sup> AstraZeneca Canada Inc. v. Canada (Minister of Health), [2006] 2 S.C.R. 560 (Can.); Bristol-Myers Squibb Co. v. Canada, [2005] 1 S.C.R. 533 (Can.); H.R. REP. NO. 98-857, pt. 1, at 17-18 (1984); H.R. REP. NO. 98-857, pt. 2, at 5-6 (1984).

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patents used to keep generics off the market? What is the relationship between new and follow-on drugs and how a given patent may be listed on the patent register in order to delay generic entry? Finally, is it possible that the same kind of "rational ignorance" applies to drug regulators as observed for patent examiners,<sup>18</sup> and if so, what would be the implications of a low standard of drug approval for public health compared to a low standard of patent approval?

Questions of this nature help to identify regulatory, economic, and drug development preferences for different drug classes, how these preferences interact to shape the outcomes and outputs of pharmaceutical innovation policy, and how they impact drug pricing and drug expenditures by governments, consumers, and other institutional payers. An empirical framework for the harmonized assessment of drug approval, drug patents and related chemical components would be valuable in this regard.

One of the major determinants of the availability and costs of brand and generic drugs in many developed nations, including the United States, Canada, Mexico, Australia, China, and other nations is the creation of pharmaceutical linkage laws, which tie generic market entry to patents associated with the drugs targeted for generic substitution. Indeed, pharmaceutical linkage brings together the twin concerns over the social value of new and follow-on drugs and ever-greening of older blockbusters under one roof. Approval and patenting of poorly innovative follow-on drugs are now recognized to have the capacity to significantly delay generic entry, even though this result runs contrary to the stated goals of the original Hatch Waxman linkage regime.<sup>19</sup> This result is brought about, in large part, via the provision under linkage for brand firms to list patents that are deemed legally relevant to an existing drug on a patent register.<sup>20</sup> Under linkage laws, generic firms must litigate all listed patents in order to gain market entry prior to the date on which all patents listed on the patent register expire e.g., the patent with the latest expiration date expires. Thus, the ability of brand firms to list multiple relevant patents against

<sup>&</sup>lt;sup>18</sup> Lemley, *supra* note 4, at 1495.

<sup>&</sup>lt;sup>19</sup> FED. TRADE COMM'N, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY 39-40 (2002), http://www.ftc.gov/os/2002/07/generic drugstudy.pdf, [hereinafter FTC 2002]. *See HORE, supra* note 13, at 5-11 (discussing data in the context of U.S. and Canadian linkage); Caffrey & Rotter, *supra* note 13, at 13–14. Bouchard 2011, *supra* note 14.

<sup>&</sup>lt;sup>20</sup> Caffrey and Rotter, *supra* note 13, at 14; HORE, *supra* note 13; Bouchard 2009, *supra* note 9; C. Scott Hemphill & Mark Lemley, *Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act*, ANTITRUST LJ. (forthcoming 2011) (manuscript 19) (Stanford Law and Economics Olin Working Paper No. 405, 2011; Columbia Law and Economics Working Paper No. 391, 2011).

the generic product, in turn, sows the seeds for the growth of product-patent clusters over time, where the ability of brand firms to delay generic entry is proportional or greater than the sum of chemically or functionally related drug approvals, drug patents, and patents listed on the patent register (referred to as the Orange Book in the U.S. and the Patent Register in Canada). An ancillary effect of this scenario is the claim that the more firms focus research and development (R&D) and marketing resources on follow-on drugs, the less their ability to expend resources in furtherance of truly pioneering drug products.<sup>21</sup> To the extent that relatively low standards for drug approval, patent grant, and patent listing restrain generic entry while also reducing the production of new and innovative drugs, the public policy underpinning pharmaceutical innovation and drug regulation is offended.<sup>22</sup>

In this light, the legal duty on governments set out in representative patent law, food and drug law, and public health law to be reasonable and fair to brand and generic firms and the public assumes importance.<sup>23</sup> This duty is said to arise in order to avoid unfairness as a result of improperly circumscribed patent law.<sup>24</sup> Leading courts have said that there is a high economic cost attached to the legal uncertainty that arises from poorly circumscribed patent scope in the public health sphere and that it is the proper policy of patent law to keep it to a minimum.<sup>25</sup> This balancing of public and private interests

<sup>24</sup> Ron A. Bouchard, Should Scientific Research in the Lead-up to Invention Vitiate Obviousness Under the Patented Medicines (Notice of Compliance) Regulations: To Test or Not to Test?, 6 CAN. J. L. & TECH. 1 (2007).

 $^{25}$  Free World Trust v. Electro Sante Inc., [2000] 2 S.C.R. 1024 ¶ 42 (Can.) (finding that "the patent system is designed to advance research and development and to encourage broader economic activity...however if competitors fear to tread in the vicinity of the patent because its scope lacks a reasonable measure of precision and certainty... [the patent] becomes a public nuisance."); R.C.A. Photophone Ltd. v. Gaumont-British Picture Corp. [1936], 53 R.P.C. 167, 195 (C.A.) (finding that uncertainty in the scope of patent discourages competition).

Potential competitors are deterred from working in areas that are not in fact covered by the patent even though costly and protracted litigation (which in the case of patent disputes can be very costly and protracted indeed) might confirm that what the competitors propose to do is entirely lawful. Potential investment is

<sup>&</sup>lt;sup>21</sup> Hollis, *supra* note 10, at 1187, 1189; Arjun Jayadev & Joseph Stiglitz, *Two Ideas to Increase Innovation and Reduce Pharmaceutical Costs and Prices*, HEALTH AFFAIRS, w165, w166 (Dec. 17, 2007), *available at* http://content.healthaffairs.org/content/28/1/w165.full.

<sup>&</sup>lt;sup>22</sup> Bouchard 2011, *supra* note 14, at 415.

<sup>&</sup>lt;sup>23</sup> Whirlpool, [2000] 2 S.C.R. ¶ 49g; Consolboard Inc. v. MacMillan Bloedel Ltd., [1981] 1 S.C.R. 504, 520 (Can.); Canada Gazette Part I, 138 CAN. GAZETTE 50, 3714 (2004); Canada Gazette Part I 140 CAN. GAZETTE 24, 1601 (2006); Canada Gazette Part II, 142 CAN. GAZETTE 13, 1390, 1588 (2008).

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creates a well-defined risk zone by respecting the terms of the traditional patent bargain in the race to win the innovation sweepstakes.<sup>26</sup> Jurisprudence to the effect that patents of uncertain scope are tantamount to a public nuisance,<sup>27</sup> including in the pharmaceutical sector specifically,<sup>28</sup> therefore provides a unique focal point for balancing public and private interests inherent to the patent bargain, the balancing of patent law with food and drug law through linkage laws, and regulatory preferences relating to new and follow-on drugs.

Considerations such as those described above motivate the present study. The broad objective of this work was to develop an evidence-based and novel innovation index to qualify intellectual property rights associated with pharmaceutical products. The goal was to create a single index applicable to new and follow-on brand drugs as well as to generic drugs. To this end, it was necessary to first quantitatively analyze in detail the approval, patenting and chemical characteristics of drugs approved in a large cohort as well as drugs vetted by the market and regulators to be the most profitable. We analyzed all classes of drugs recognized by domestic regulators in various new and followon drug classes as well as generic drugs. To this end we updated our previous analyses of 2,122 approvals associated with 608 drugs granted between 2001 and 2008.<sup>29</sup> In addition, a cohort of 375 approvals associated with 95 drugs was further assessed that had been vetted by the market to be the most profitable drugs sold domestically.<sup>30</sup> This encompassed further analysis of 5.011 patents, and 130 chemical components claimed in these patents. As this was the first time that approval, patenting and chemical components were brought together in a single analysis at this level of drug class discrimination, the database is referred to as "harmonized."

As noted above, a major purpose of this study was to develop a unified

<sup>28</sup> Farbwerke v. Commissioner, [1966] S.C.R. 604, 617 (Can.).

lost or otherwise directed. Competition is "chilled." The patent owner is getting more of a monopoly than the public bargained for. There is a high economic cost attached to uncertainty and it is the proper policy of patent law to keep it to a minimum.

Id.

<sup>&</sup>lt;sup>26</sup> R. v. Nova Scotia Pharm. Soc'y, [1992] 2 S.C.R. 606 ¶ 43 (Can.); *Free World Trust*, [2000] 2 S.C.R. ¶ 41.

<sup>&</sup>lt;sup>27</sup> Free World Trust, [2000] 2 S.C.R. 1024 ¶ 42; see also RCA Photophone, [1936], 53 R.P.C. 167, 195.

<sup>&</sup>lt;sup>29</sup> Bouchard 2009, *supra* note 9. See also, Monika Sawicka & Ron A. Bouchard, Empirical Analysis of Canadian Drug Approval Data 2001-2008: Are Pharmaceutical Players "Doing More With Less"?, 3 MCGILL J.L. & HEALTH 85 (2009).

<sup>&</sup>lt;sup>30</sup> Bouchard 2010, *supra* note 14.

method to collect, compare and quantify regulatory approval data from multiple cohorts of new and follow-on drugs that encompassed all drug classes enumerated, described and prioritized by domestic drug regulators. A related purpose was to address uncertainty in the literature regarding approval nomenclature, such as whether certain drugs should be called new or follow-on, follow-on or Me Too, and whether the Me Too and First in Class designations refer only to drugs approved via the new drug approval route or should also refer to drugs that are line extensions. Finally, a major objective of this work was to provide quantitative data on drug approvals, patenting and chemical components for analysis using the qualitative index for pharmaceutical products described in the companion article.<sup>31</sup>

#### III. METHODS

#### A. Drug Approval Nomenclature

Federal governments in most developed nations have worked intensely toward regulatory harmony over the last two decades, particularly with respect to the emerging "lifecycle" model of drug regulation.<sup>32</sup> Therefore, the regulatory framework for drug approval in Canada parallels that of the United States Food and Drug Administration (FDA) and European Medical Association (EMEA).<sup>33</sup> In all nations, brand-name (brand) drugs submitted through "New" or "Supplementary" pathways, can be classified as "First in Class," "Me-Too," or "Line Extensions," under appropriate circumstances undergo some form of "expedited review," and can contain a "New Chemical Entity" (NCE) or "New Active Substance" (NAS). Similarly, generic firms may submit applications for "Abbreviated" review and may also have "Supplementary" or line extension approvals.

In Canada, brand sponsors may file a New Drug Submission (NDS)<sup>34</sup> containing data relating to drug safety, efficacy, and quality to gain regulatory

<sup>&</sup>lt;sup>31</sup> QIP II Companion Paper, *supra* note 8.

<sup>&</sup>lt;sup>32</sup> Eichler et al. *supra* note 2; Bouchard & Sawicka, *supra* note 12.

<sup>&</sup>lt;sup>33</sup> HEALTH CANADA, BLUEPRINT FOR RENEWAL: TRANSFORMING CANADA'S APPROACH TO REGULATING HEALTH PRODUCTS AND FOOD 14, 20, 38-39 (2006), *available at* http://www.hc-sc.gc.ca/ahc-asc/alt\_formats/hpfb-dgpsa/pdf/hpfb-dgpsa/blueprint-planeng.pdf. *See also* Lemmens & Bouchard, *supra* note 12. *See generally* Patricia I. Carter,

Federal Regulation of Pharmaceuticals in the United States and Canada, 21 LOY. L.A. INT'L & COMP. L. REV. 215 (1999).

<sup>&</sup>lt;sup>34</sup> Lemmens & Bouchard, *supra* note 12. *See also* Food and Drug Regulations, CRC, ch. 870, at § C.08.002(1)(a) (2009). The Food and Drug Regulations are propagated under the general authority of the Food and Drugs Act, RSC, ch. F-27 (1985).

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approval (referred to as a Notice of Compliance or NOC).<sup>35</sup> A Supplemental New Drug Submission (SNDS) may be filed for changes to a drug already marketed by that sponsor.<sup>36</sup> These submissions include amendments to drug dosage, strength, formulation, manufacture, labeling, route of administration, or indication.<sup>37</sup> Products associated with an SNDS are typically referred to as line extensions, referring to the fact that they are extensions of already marketed products.<sup>38</sup> Generic manufacturers may submit an Abbreviated New Drug Submission (ANDS) to obtain an NOC requiring that generic drugs be pharmaceutically equivalent to the reference brand product.<sup>39</sup> Generic sponsors may also submit Supplemental Abbreviated New Drug Submissions (SANDS) when changes are made to a drug already on the market. Consequently, both brand-name and generic firms can make both "new" and "supplemental" (follow-on or line extension) submissions.

Drugs identified by regulators as meeting "sufficient medical need" to undergo some form of priority review are considered by many to be innovative drugs.<sup>40</sup> Regulators may grant approval in an expedited fashion under domestic food and drug law in two ways.<sup>41</sup> One is through Priority Review, which refers to the fast-tracking of eligible drug candidates "intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases or conditions" with an "unmet medical need or for which a substantial

<sup>&</sup>lt;sup>35</sup> Food and Drug Regulations, *supra* note 34, at § C.08.002(2); Lemmens & Bouchard, *supra* note 12, at 325. *See also* HEALTH CANADA: HEALTH PROTECTION BRANCH, PREPARATION OF HUMAN NEW DRUG SUBMISSIONS: THERAPEUTIC PRODUCTS PROGRAMME GUIDELINE (1991), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt\_formats/hpfb-dgpsa/pdf/prodpharma/prephum-eng.pdf.

<sup>&</sup>lt;sup>36</sup> Food and Drug Regulations, C.R.C. c. 870, § C.08.003 (Can.).

<sup>&</sup>lt;sup>37</sup> *Id.* § C.08.003(2). *See also* Lemmens & Bouchard, *supra* note 12, at 326.

<sup>&</sup>lt;sup>38</sup> Lexchin, *supra* note 10, at 243. *See generally* Song Hee Hong et al., *Product-Line Extensions and Pricing Strategies of Brand Name Drugs Facing Patent Expiration*, 11 J. MANAGED CARE PHARMACY 746 (2005).

<sup>&</sup>lt;sup>39</sup> The term bioequivalence refers to the requirement that the generic product must be equivalent to the already marketed 'reference product' with regard to chemistry, manufacturing, route of administration, use, and therapeutic and adverse systemic effects. *See also* Food and Drug Regulations, C.R.C., c. 870 §§ C.08.001.1, C.08.002.1(1) (defining and discussing the terms Canadian reference product and pharmaceutical equivalent).

<sup>&</sup>lt;sup>40</sup> NAT'L INST. FOR HEALTH CARE MGMT., CHANGING PATTERNS OF PHARMACEUTICAL INNOVATION 7 (2002) [hereinafter CHANGING PATTERNS]; DiMasi & Faden, *supra* note 11 at 24; DiMasi & Paquette, *supra* note 11 at 8; Frank R. Lichtenberg, *Pharmaceutical Knowledge - Capital Accumulation and Longevity, in* MEASURING CAPITAL IN THE NEW ECONOMY 237 (Carol Corrado, John Haltiwagner & Daniel Sichel eds., 2004).

<sup>&</sup>lt;sup>41</sup> See generally Bouchard & Sawicka, supra note 12, at 58–9.

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improvement in the benefit/risk profile is demonstrated."<sup>42</sup> Evidentiary requirements for safety, efficacy, and quality parallel those for non-priority submissions; the main difference is an accelerated review time.<sup>43</sup> In the second path, sponsors may be granted an "NOC with conditions" (NOC/c)<sup>44</sup> for eligible NDS or SNDS submissions directed to serious, life-threatening, or severely debilitating diseases, or conditions for which there is promising evidence of clinical effectiveness based on available data.<sup>45</sup> In addition to less onerous evidentiary requirements, the targeted review time for NOC/c approval is significantly accelerated compared to that for standard NDS review.<sup>46</sup>

The main difference with Priority Review is that NOC/c licensure is granted on the condition that the sponsor will perform additional post-market studies to confirm the alleged benefits and risks. Unless otherwise stated, for the purposes of this Article NOC/c and Priority Review pathways for approval are collapsed together under the single heading of Expedited Review (ER).

According to the literature, it is considered a hallmark of innovation for a drug to contain a novel chemical form.<sup>47</sup> This plays out in the current regulatory context in one of two ways: drugs may contain a new active substance (NAS) or have sufficient chemical novelty and use characteristics to be denoted first in class (First in Class or FIC). Previously referred to as a "new chemical entity," or NCE,<sup>48</sup> the definition of an NAS encompasses a wide range of chemically active substances, including (1) a chemical or

<sup>&</sup>lt;sup>42</sup> HEALTH CAN., GUIDANCE FOR INDUSTRY: PRIORITY REVIEW OF DRUG SUBMISSIONS 1– 2, 4 (2009), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt\_formats/hpfbdgpsa/pdf/prodpharma/priordr-eng.pdf.

<sup>&</sup>lt;sup>43</sup> Lemmens & Bouchard, *supra* note 12, at 328.

<sup>&</sup>lt;sup>44</sup> NOC/c approvals are granted pursuant to Food and Drug Regulations § C.08.004.01(1), in compliance with the conditions of use stipulated in §§ C.08.002.01, C.08.002.1, C.08.003, and C.08.005.1.

<sup>&</sup>lt;sup>45</sup> HEALTH PRODS. & FOOD BRANCH, HEALTH CAN., GUIDANCE DOCUMENT: NOTICE OF COMPLIANCE WITH CONDITIONS (NOC/c) 3 (2007), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt\_formats/hpfb-dgpsa/pdf/prodpharma/noccg\_accd-eng.pdf.

<sup>&</sup>lt;sup>46</sup> HEALTH CAN., ACCESS TO THERAPEUTIC PRODUCTS: THE REGULATORY PROCESS IN CANADA 10-11 (2006), *available at* http://www.hc-sc.gc.ca/ahc-asc/alt\_formats/hpfb-dgpsa/pdf/pubs/access-therapeutic\_acces-therapeutique-eng.pdf.

<sup>&</sup>lt;sup>47</sup> U.S.NAT'L RES. COUNCIL, COMMITTEE ON KNOWLEDGE ASSESSMENT OFFICE OF INT'L AFFAIRS, PROSPECTUS FOR NATIONAL KNOWLEDGE ASSESSMENT, 10 (1996) [hereinafter PROSPECTUS]; Fredric J. Cohen, *Macro Trends in Pharmaceutical Innovation*, 4 NATURE REV. DRUG DISCOVERY 78, 78 (2005) J. D. Kleinke, *Commentary: Much Ado About a Good Thing*, 325 Brit. Med. J. 1168, 1168 (2002).

<sup>&</sup>lt;sup>48</sup> PROSPECTUS, *supra* note 47; Cohen, *supra* note 47; Kleinke, *supra* note 47.

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biological substance that has not been previously approved for sale as a drug, (2) an isomer, derivative, or salt of a chemical substance that is already approved for sale as a drug but differs in safety and efficacy properties, or (3) a biological substance previously approved for sale as a drug that differs in molecular structure, the nature of the source material, or the manufacturing process.<sup>49</sup>

To summarize, within the "new" NDS approval route, drugs can contain a new active substance (NAS), can be approved in an expedited manner either through the Priority Review or NOC/c pathway, or may be approved as NDS drugs without any further designation. Similarly, drugs may go through the "follow-on" SNDS approval route alone or in an expedited manner via the Priority Review and NOC/c pathways. Finally, drugs generic drugs are approved in the traditional abbreviated (ANDS) or follow-on (SANDS) routes. A summary of drug approval pathways is provided in Table 1.

Firm Type	New Drugs	Follow-On Drugs
A. BRAND	NDS NDS NAS NDS PR NDS NOC/c	SNDS SNDS PR SNDS NOC/c
B. GENERIC	:	ANDS SANDS

# Table 1. Summary of Drug Approval Pathways

Further discrimination of drug classes is typically made by regulators, scholars and commentators between drugs that are deemed to be first in class (First in Class or FIC) and me too (Me Too) drugs. First in Class drugs are those that consist of either a new family of active ingredient(s), comprising NAS drugs,<sup>50</sup> or old active ingredient(s) used for the treatment of a new

<sup>&</sup>lt;sup>49</sup> DRUGS DIRECTORATE, HEALTH CAN., POLICY ISSUE NEW ACTIVE SUBSTANCE (1991), available at http://www.hc-sc.gc.ca/dhp-mps/alt\_formats/hpfb-dgpsa/pdf/prodpharma/nas\_nsa\_pol-eng.pdf [hereinafter DRUGS DIRECTORATE]; HEALTH CAN., DRUGS AND HEALTH PRODUCTS – NOC DATABASE TERMINOLOGY, (2010) available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/noc-acc/term\_noc\_acc-eng.php.

<sup>&</sup>lt;sup>50</sup> DRUGS DIRECTORATE, *supra* note 49.

indication. A drug is First in Class if there is no other drug on the market that belongs to the same compound family that is used for the same indication.<sup>51</sup> By contrast, Me Too drugs are those that offer "important therapeutic options," but that may have little or no change to the benefit: risk profile.<sup>52</sup> Me Too drugs are comparable to other drugs in terms of compound and indication.<sup>53</sup> Like drugs that undergo expedited review and those with the NAS designation, drugs that are FIC are considered to be indicative of strong innovation,<sup>54</sup> including when they are follow-on drugs.<sup>55</sup>

Drugs approved through both new and follow-on submission routes can be FIC or Me Too. For the new drug approval route, NDS FIC drugs are those that contain either an NAS or are directed to a new use (i.e. indication). NDS Me Too drugs by contrast neither contain a new ingredient nor are directed to a new use, but instead have an improved benefit-risk profile. For the traditional line extension SNDS route, relatively small changes to existing chemical structures such as salts or isomers may still yield FIC or Me Too designations. The difference is that while both SNDS FIC and Me Too drugs can cover new chemical forms,<sup>56</sup> only drugs directed to a new use may be deemed to be an SNDS FIC drug.<sup>57</sup> Those that do not are Me Too drugs.<sup>58</sup> Because even a follow-on FIC drug must be directed to a new use as opposed to just a new chemical form with altered benefit: risk, a higher level of innovation is ascribed to SNDS FIC drugs as opposed to Me Too drugs.<sup>59</sup> The characteristics of FIC and Me Too drugs are summarized in Table 2.

<sup>&</sup>lt;sup>51</sup> Letters between author, David K. Lee, Dir., Office of Legislative and Regulatory Modernization, Health Can., Dr. Maurica Maher, Senior Scientific Advisory, Progressive Licensing Project, Health Can., and Lesley Brumell, Supervisor, Submission and Info. Policy Div., Health Can. (April-July 2008) (on file with author) [hereinafter Health Canada Personal Communications].

<sup>&</sup>lt;sup>52</sup> Id.

<sup>&</sup>lt;sup>53</sup> Id.

<sup>&</sup>lt;sup>54</sup> Cohen, *supra* note 47.

<sup>&</sup>lt;sup>55</sup> DiMasi & Faden, *supra* note 11, at 27.

<sup>&</sup>lt;sup>56</sup> Health Canada Personal Communication, *supra* note 51.

<sup>&</sup>lt;sup>57</sup> Id.

<sup>&</sup>lt;sup>58</sup> Id.

<sup>&</sup>lt;sup>59</sup> For a comparison of Canadian and World Health Organization First in Class and Me Too classifications schemes, see Sawicka & Bouchard, *supra* note 29, at 108 (comparing Tables 2 and 5).

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Table 2. Designation of New and Follow-on First in Class and Me Too Drugs

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

The final category of drug approvals investigated pertains to the most innovative (MI) drugs developed by brand firms. The designation NDS MI is used based on the methodology for new drugs elucidated in our Berkeley study.<sup>60</sup> As discussed in detail there, merely containing an NAS is an insufficient basis for designating a drug as pioneering or strongly innovative because there is ample room in the definition for minor changes to previously approved medical ingredients, including salts, esters, solvates, polymorphs, and enantiomers. Similarly, FIC drugs do not, of themselves, constitute pioneering products based on the observation that these can also be follow-on versions of previously marketed products containing slightly modified medical ingredients or directed to new uses within a therapeutic class. The same conclusion applies to expedited review drugs where these need only be directed to drugs demonstrating moderate clinical improvement over existing therapies. The definition that is the most reasonable in terms of a plain and obvious reading of the enabling statute and that accords with historical pharmaceutical linkage policy is that truly pioneering drugs are those that (a) are approved via the new drug approval pathway (NDS), (b) contain an NAS, (c) undergo some form of expedited review (ER), and (d) are directed to a FIC therapy.

#### B. Cohort, Indicator and Class Terminology

Drug approval, drug patenting, and patent listing data were identified, collected and analyzed as described previously. Briefly, new and follow-on drug approvals were obtained using data publicly reported on the Health Canada website and collated and assessed using the methodology described in

<sup>&</sup>lt;sup>60</sup> Bouchard 2009, *supra* note 9, at 1492-93.

Sawicka and Bouchard.<sup>61</sup> This study assessed 608 new and follow-on drugs in a cohort of 2,166 approvals granted by regulators between 2001 and 2008. This database was updated in November 2010, and was found to contract to 2,087 approvals owing to pruning over time by regulators. We observed no meaningful difference between the fraction of new and follow-on drugs and sub-classes between the two data sets (compare Fig. 1 below with Fig. 3 in Ref.<sup>62</sup>). Data reported here are only for the updated set of 2,087 approvals, referred to henceforth as the Total Approval Cohort.

Data are also reported for a second drug approval cohort comprising 95 drugs which had a total of 347 approvals. This group of drugs differed from the Total Approval Cohort in that it represented the 95 most profitable drugs approved in Canada over the test period 2001-2008.<sup>63</sup> As these data relate only to the most profitable drugs, this data set is referred to as the MP Approval Cohort.

Patents associated with the MP Approval Cohort were obtained from the Canadian Intellectual Property Office website. They were collated, assessed and cross-referenced with data obtained from the U.S. Patent and Trademark Office using the Boolean search strings, patent tree, patent classification, and other methods described in our pilot study of 16 drugs,<sup>64</sup> and our later follow-up study of 95 drugs updated to November 2010.<sup>65</sup> We identified 5,011 patents associated with the MP Approval Cohort. Patents listed on the Canadian Patent Register (analogous to the Orange Book under Hatch Waxman) were also obtained and analyzed using the methods described in our Berkeley and Northwestern studies. All patents analyzed in this study are related to the MP Approval Cohort, and thus are referred to as referred to as the MP Patent Cohort.

Identical methods to the MP Patent Cohort were used for analysis of chemical components associated with drug approvals. Chemical components were identified from the patents identified in our Northwestern study. The 130 distinct chemicals identified in patents associated with the MP Patent Cohort are referred as the MP Chemical Cohort. A summary of Cohort terminology is provided in Table 3.

<sup>&</sup>lt;sup>61</sup> Sawicka & Bouchard, *supra* note 29, at 88-103.

<sup>&</sup>lt;sup>62</sup> Bouchard 2010, *supra* note 14, at 195.

<sup>&</sup>lt;sup>63</sup> *Id*. at 184.

<sup>&</sup>lt;sup>64</sup> Bouchard 2009, *supra* note 9, at 1482-86.

<sup>&</sup>lt;sup>65</sup> Bouchard 2010, *supra* note 14, at 184-192.

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# Table 3. Classification Scheme for Data Cohorts

Cohort	Description
A. TOTAL APPROVAL COHORT	All 2,087 approvals granted between 2001-2008
B. MP APPROVAL COHORT	Sub-group of 95 of the most profitable drugs approved between 2001-2008
C. MP PATENT COHORT	5,011 patents associated with the most profitable approval sub-group
D. MP CHEMICAL COHORT	130 chemicals components claimed in patents associated with the most profitable sub-group

A note is relevant regarding the novelty of the methods and analytic framework described in this Article. In our previous work, we identified and analyzed various drug approval, patenting and patent listing metrics alone or in combination with one another. However, to this point we had not parsed all classes of approvals, patenting and listing into their most detailed classes (eg both NDS and SNDS classes of FIC, ME Too, ER and residual indicators as well as NDS NAS and NDS MI classes). Nor did we obtain the same granularity of measurement across approval and patenting cohorts or identify or measure the chemical components identified in patents associated with drugs. In addition, to this point we had only employed the analysis of the NDS MI class in our pilot study of 16 drugs conducted using data collected from 2001 to 2008. Here we extend this analysis to a database of 95 drugs updated to November 2010. Moreover, assessment of drug chemical components is undertaken here for the first time. This was done in order to get some sense empirically of the degree to which brand and generic firms are focusing their efforts on cluster-based drug development.

As a result, this is the first study by our group that collects and analyzes approval, patenting, patent listing, and chemical data for brand and generic drugs at all levels of new (NDS) and follow-on (SNDS; Generic) detail in the largest cohort for which we have studied all indicators to date (n= 95 drugs). It is also the first study undertaken which harmonizes these measurements in a single analysis of drug category, drug class, and sub-class. The harmonized approval, patenting and chemical data are particularly important because they provide the quantitative basis for the application of the innovation index

framework elucidated in the companion paper.66

For purposes of this Article, a "cohort" refers to a data set, of which there are four in this study: Total Approval, MP Approval, MP Patent, and MP Chemical Cohorts. By contrast, "indicator" refers to the characteristic being measured, and we examined three in this study: approvals, patents, chemicals. Each of the three indicators is measured in the thirteen classes of new and follow-on drugs described above. These include NDS drugs that can be classified as Me Too drugs (NDS Me Too), contain an NAS (NDS NAS), have a FIC designation (NDS FIC), have gone through one of the two ER pathways (NDS ER), represent the most innovative class of new drugs (NDS MI), or simply go through the new drug submission pathway with no further class designation (NDS). Similarly, follow-on drugs can be SNDS drugs in and of themselves (SNDS) or drugs approved via the supplemental pathway that can be classified as Me Too drugs (SNDS Me Too), have a FIC designation (SNDS FIC), or have gone through one of the two ER pathways (SNDS ER). Finally, generic drugs can be assessed as a total group but can also be assessed as having gone through their own versions of new (ANDS) and supplemental (SANDS) approval pathways. In total, this includes 13 classes of new and follow-on drugs, described in relation to each of the four cohorts.

In the numerical framework provided in the Results and interpreted in the Discussion, the NDS-Total, SNDS-Total and Generic-Total calculations are absolute. Together these three types of approvals will always total 100% of observed approvals, patents and chemicals across indicators. Similarly, drugs can only be FIC or Me Too, but not both, and MI and NAS drugs are only approved via the NDS approval route. However, all other drugs can variously occupy FIC, Me Too, and ER sub-classes within NDS and SNDS categories. This has two effects in the data analysis and presentation. First, the percentile values within a given NDS or SNDS category do not add up to 100% due to the overlap between classes. Second, the largest numerical bins are for the four cohorts, followed by new and follow-on categories, followed by the various new and follow-on classes. It is necessary to study all classes across indicators, as regulators and the courts refer to each class in publicly disclosed regulatory documents and judicial decisions, as does the pharmaceutical and innovation literature. The nomenclature for all new and follow-on drugs analyzed in this Article is summarized in Table 4.

<sup>&</sup>lt;sup>66</sup> QIP II Companion Paper, *supra* note 8, at 21-22.

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## Table 4. Classification Scheme for New and Follow-On Drugs

Firm Type	New Drugs	Follow-On Drugs
A. BRAND	NDS NDS Me Too NDS NAS NDS FIC NDS ER	SNDS SNDS Me Too SNDS FIC SNDS ER
B. GENERIC	-	ANDS SANDS

### C. Data Analysis

Drug approval, drug patenting, patent listing data were collected, statistically analyzed, and graphed as described previously,<sup>67</sup> using a combination of Excel<sup>®</sup> (Microsoft. Corp., Redmond, WA), Access<sup>®</sup> (Microsoft. Corp., Redmond, WA), GraphPad Prism<sup>®</sup> (Graphpad Software Inc. La Jolla, CA), and SigmaPlot<sup>®</sup> (Systat Software, Inc. San Jose, CA). Chemical data were collected, statistically analyzed, and graphed using the same methods. Approval data were obtained from the Health Canada website, patent and chemical data were obtained from Canadian (CIPO) and U.S. (USPTO) patent databases. Patent listing data were obtained from the Canadian Patent Register website maintained by Health Canada and cross-referenced using the Federal court database.

#### **IV. RESULTS**

#### A. Total Approval Cohort

Drug approvals were first assessed in a cohort of 2,087 approvals granted by drug regulators between 2001 and 2008 updated to November 2010 as described in the Methods. Approvals are referred to domestically as Notices of Compliance (NOCs). 2001 was taken as the starting point for analysis, as major amendments to the nation's food and drug legislation and regulations

<sup>&</sup>lt;sup>67</sup> Sawicka & Bouchard, *supra* note 29; Bouchard 2009, *supra* note 9; Bouchard 2010, *supra* note 14.

were made at that time which affected both the goals and mechanism of national drug regulation.<sup>68</sup>

As outlined in the Methods and summarized in Tables 1-4, approvals were analyzed across numerous classes within the broader categories of "new" and "follow-on" drugs. This included approvals in the new drug approval route directed to FIC drugs (NDS FIC), Me Too drugs (NDS Me Too), drugs containing an NAS (NDS NAS), drugs undergoing one of the two pathways for expedited review (NDS ER) and drugs deemed to be the most innovative (NDS MI). Drugs moving through the new drug approval route that did not have an extra designation (NDS) were also studied. Line extension drugs approved via the follow-on pathway were studied alone (SNDS) or in conjunction with FIC (SNDS FIC), Me Too (SNDS Me Too), and ER (SNDS ER) designations. Finally generic drugs undergoing conventional (ANDS) and follow-on (SANDS) abbreviated review were studied.

TYPE OF APPROVAL	DRUG APPROVALS						
	Updated Full Data Set	Percent Submission Type	Percent Brand Type	Percent Total			
I. BRAND SUBMISSIONS							
A. New Drug Submissions							
NDS – Total	311	100	22.8	14.9			
NDS-FIC	65	20.9	4.8	3.1			
NDS-Me Too	245	78.8	18.0	11.7			
NDS- NAS	130	41.8	9.6	6.2			
NDS-ER	47	15.1	3.5	2.3			
NDS- MI	22	7.0	1.6	1.1			
B. Follow-On Submissions							
SNDS- Total	1049	100	77.2	50.3			
SNDS-FIC	73	6.9	5.4	3.5			
SNDS-Me Too	976	93.0	71.2	46.8			
SNDS-ER	56	5.3	4.1	2.7			
C. Total Brand NOCs	1360		100	65.2			
II. GENERIC SUBMISSIONS	727	100		34.8			
ANDS	580	79.8					
SANDS	147	20.2					
III. TOTAL NOC	2087			100			
IV. TOTAL DRUGS	608						
V. NOC/DRUG	3.5						

#### Table 5: New and Follow-On Data for Total Approval Cohort

<sup>&</sup>lt;sup>68</sup> Sawicka & Bouchard, *supra* note 29, at 107.

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In addition to the raw number of approvals in each class, approvals were normalized for submissions within NDS and SNDS categories, as a percent of brand approvals, and as a percent of total brand and generic approvals. This analytical scheme is repeated for the Total Approval Cohort (Table 5), the MP Approval Cohort (Table 6), the MP Patent Cohort (Table 7) and the MP Chemical Cohort (Table 8). Table 9 summarizes the similarities and differences in data pertaining to new and follow-on drugs in the three approval groups (the original 2009 Berkeley analysis, the updated 2010 Total Approval Cohort and the updated MP Approval Cohort), as well as new and follow-on FIC and Me Too drugs. Finally, Table 10 presents two types of data for all approvals studied. The first is a general comparison of (1) the fraction of approvals expressed as rank orders that were new and follow-on in nature between the original data for 2,122 approvals granted between 2001 and 2008 described in our in our Berkeley Article (2009), (2) this data set updated in 2010 and corrected to reflect the new value of for 2,087 approvals associated with 608 drugs (Total Approval Cohort), and (3) a sub-set of 347 approvals associated with 95 of the most profitable drugs (MP Approval Cohort) also updated to 2010. The second set of values compares NDS FIC, SNDS FIC, NDS Me Too and SNDS Me Too approval classes across the three data sets. The purpose of this analysis is to demonstrate the consistency of the fraction of new and follow-on approvals over time while also highlighting the changing fractions of approvals for in the new and follow-on FIC and Me Too drug classes.



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**Fig 1. Profile of Pharmaceutical Innovation between 2001-2008 for Total Approval Cohort.** *a* New v. follow-on approvals. Of total drugs approved over the test period, 15% constituted New Drug Submissions ( $\bullet$ ; NDS) while 85% were for "follow-on" drugs ( $\bullet$ ; SNDS, ANDS and SANDS). *b* Brand-name v. Generic approvals. Of all drugs approved during the test period, 65% of approvals were granted to brand-name drug companies ( $\bullet$ ; NDS and SNDS) and 35% to generic companies ( $\bullet$ ; ANDS and SANDS). *c* Details of approvals. Of approvals, 6.6% were for NDS and SNDS "First in Class" ( $\bullet$ ; FIC) drugs while 58.5% were for NDS and SNDS "Me-Too" drugs ( $\bullet$ ). *d* Most innovative drugs. While 6.2% of approvals during the test period were directed to NDS New Active Substances ( $\bullet$ ; NAS), 3.1% of NDS approvals were directed to FIC drugs, and 2.3% of NDS submissions were approved over the period 2001-2008 contained an NDS NAS, underwent some form of NDS ER and were directed to NDS FIC therapies ( $\bullet$ ). Areas are approximations of calculated means for the entire test period. Regulatory data from Bouchard et al. 2009 24 *BTLJ* 1461 were updated in November 2010 using revised data published by the federal government, with small differences in nomenclature (separation of NDS and SNDS FIC and Me Too drugs).

Fig 1. illustrates the profile of pharmaceutical innovation between 2001 and 2008 for the Total Approval Cohort. Fig. 1a shows the fractions of drug approvals in new and follow-on approval classes. Of total drugs approved over the test period, 15% constituted New Drug Submissions (•; NDS) while 85% were for "follow-on" drugs (•; SNDS, ANDS and SANDS). Fig. 1b presents

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data pertaining to brand and generic approvals. Of all drugs approved in the Total Approval Cohort, 65% of approvals were granted to brand-name drug companies (•; NDS and SNDS) and 35% to generic companies (•; ANDS and SANDS).

A more nuanced analysis of approvals in the Total Approval Cohort is provided in Fig. 1c, which demonstrates that 6.6% of approvals were for NDS and SNDS FIC drugs ( $\bigcirc$ ; FIC) drugs while 58.5% were for NDS and SNDS Me-Too drugs ( $\bigcirc$ ).

The details of the most innovative drugs are provided in Fig. 1d. The data show that while 6.2% of approvals during the test period were directed to NDS New Active Substances (•; NAS), 3.1% of NDS approvals were directed to FIC drugs, and 2.3% of NDS submissions were approved under an expedited review process (•; Priority Review and NOC/c), only 1.1% of all drugs approved over the period 2001-2008 contained an NDS NAS, underwent some form of NDS ER and were directed to NDS FIC therapies (•). As indicated in the legend, the areas of the "egg diagrams" are visual approximations of calculated means for the entire test period provided in Table 5. The same is true for Figs. 2-4.

As noted *supra*, the raw data giving the absolute number of approvals in the cohort, as well as the fraction of NDS and SNDS submission classes and total brand approvals in the cohort are given in Table 5. These data are discussed in greater detail in the Discussion.

#### B. MP Approval Cohort

The analysis of approvals in the MP Approval Cohort and all classes of NDS, SNDS, ANDS, and SANDS approvals tracks that for the Total Approval Cohort. Accordingly, Fig. 2a provides the fractions of drug approvals in new and follow-on approval classes. Of total drugs approved over the test period, 15% constituted New Drug Submissions (•; NDS) while 85% were for "follow-on" drugs (•; SNDS, ANDS and SANDS). As noted in Table 6, this is essentially identical to the Total Approval Cohort, despite the differences in number of approvals (2,087 v. 345) and "most profitable" character of the MP Approval Cohort.



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Fig 2. Profile of Pharmaceutical Innovation between 2001-2008 for Most Profitable Approval Cohort. *a* New v. follow-on approvals. Of total drugs approved over the test period, 15% constituted New Drug Submissions ( $\bigcirc$ ; NDS) while 85% were for "follow-on" drugs ( $\bigcirc$ ; SNDS, ANDS and SANDS). *b* Brand-name v. Generic approvals. Of all drugs approved during the test period, 80% of approvals were granted to brand-name drug companies ( $\bigcirc$ ; NDS and SNDS) and 20% to generic companies ( $\bigcirc$ ; ANDS and SANDS). *c* Details of approvals. Of, 16% were for NDS and SNDS "First in Class" ( $\bigcirc$ ; FIC) drugs while 65% were for NDS and SNDS "Me-Too" drugs ( $\bigcirc$ ). *d* Most innovative drugs. While 11.2% of approvals during the test period were directed to NDS New Active Substances ( $\bigcirc$ ; NAS), 5.7% of NDS approvals were directed to FIC drugs, and 12.7% of NDS submissions were approved over the period 2001-2008 contained an NDS NAS, underwent some form of NDS ER and were directed to NDS FIC therapies ( $\bigcirc$ ). Areas are approximations of calculated means for the entire test period.

Fig. 1b presents data pertaining to brand and generic approvals. Of drugs approved in the Total Approval Cohort, 80% of approvals were granted to brand drug companies (•; NDS and SNDS) and 20% to generic companies (•; ANDS and SANDS). The increase in brand approvals compared to generics in the MP Approval Cohort compared to the Total Approval Cohort is not surprising in light of the most profitable designation for the cohort. Even

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so, as discussed in greater detail below, the number of approvals for generic products in this cohort is nevertheless surprisingly significant. The presence of significant number of approvals in the MP Approval Cohort likely reflects the genericization of a significant fraction of brand drugs over the course of the test period.

The more nuanced analysis of new and follow-on approvals is provided in Fig. 2c, demonstrating that 16% of approvals were for NDS and SNDS FIC drugs (•; FIC) drugs while 65% were for NDS and SNDS Me-Too drugs (•). The fraction of total approvals for FIC drugs jumped from 6.6% to 16%, an increase of close to 150% from the Total Approval Cohort. By contrast, the fraction of Me Too drugs remained relatively constant from 59% in the Total Approval Cohort to 65% in the MP Approval Cohort. While the combined new and follow-on fractions of Me Too drugs remained relatively constant, the distribution of these drugs within NDS and SNDS classes did change considerably (Table 6). For example, the percent NDS Me Too approvals went from 3.1% in the Total Approval Cohort to 5.7% in the MP Approval Cohort, an increase of 80% over the Total Approval Cohort value, while the fraction of NDS Me Too approvals went from 47% to 56%, representing a smaller but significant increase of 20%. As with the Total Approval Cohort, shifts in normalized and raw data between cohorts are parsed in greater detail in the Discussion section.

TYPE OF APPROVAL	DRUG APPROVALS						
	Most Profitable Data Subset	Percent Submission Type	Percent Brand Type	Percent Total			
I. BRAND SUBMISSIONS							
A. New Drug Submissions							
NDS – Total	51	100	18.2	14.7			
NDS-FIC	20	39.2	7.17	5.7			
NDS-Me Too	31	60.7	11.1	8.9			
NDS- NAS	39	76.4	13.9	11.2			
NDS-ER	44	86.2	15.8	12.7			
NDS- MI	20	39.2	7.17	5.7			
B. Follow-On Submissions							
SNDS- Total	228	100	81.7	65.7			
SNDS-FIC	34	14.9	12.1	9.7			
SNDS-Me Too	194	85.1	69.5	55.9			
SNDS-ER	46	20.2	16.5	13.2			
C. Total Brand NOC	279		100	80.4			
D. Total Drug	95						
E. NOC/Drug	2.9						
II. GENERIC SUBMISSIONS	68	100	24.3	19.6			
ANDS	57	83.8					
SANDS	11	16.2					
III. TOTAL NOC	347			100			

#### Table 6: New and Follow-On Data for MP Approval Cohort

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The details of the most innovative drugs are provided in Fig. 2d, which shows that 11.2% of all approvals during the test period were directed to NDS New Active Substances (•; NAS), 5.7% of NDS approvals were directed to FIC drugs, and 12.7% of NDS submissions were approved under an expedited review process (•; Priority Review and NOC/c). This yields a value of 5.7% of total drugs approved over the period 2001-2008 that contained an NDS NAS, underwent some form of NDS ER and were directed to NDS FIC therapies (•). These values, while small, represent a substantial change from those in the Total Approval Cohort. The values for NDS NAS, NDS ER, NDS FIC, and NDS MI increased by 180%, 552%, 184%, 520%, respectively. Thus, while the approval in the NDS MI value in the MP Approval Cohort was driven primarily by the substantial increase in NDS ER approval.

#### C. MP Patenting Cohort

Data for the MP Patenting Cohort and all classes of NDS, SNDS, ANDS, and SANDS approvals are provided in Fig. 3 and Table 7. The percentages of total patents associated with the MP Approval Cohort in new and follow-on drug classes are given in Fig. 3a. Of total patents associated with the most profitable cohort over the test period, 24% were associated with drug approved in the New Drug Submission pathway (•; NDS) while 76% were associated with drugs approved via the follow-on pathway (•; SNDS, ANDS and SANDS). This represents the first change from the 85:15 ratio observed in the Total Approval Cohort and the MP Approval Cohort.

TYPE OF APPROVAL				
	Patents (No.)	Percent Submission Type	Percent Brand	Percent Total
I. BRAND SUBMISSIONS				
A. New Drug Submissions				
NDS - Total	1182	100	31.4	23.6
NDS-FIC	550	46.5	14.6	11
NDS-Me Too	742	62.8	19.7	14.8
NDS- NAS	995	84.2	26.5	19.8
NDS-ER	1049	88.7	27.9	20.9
NDS- MI	550	46.5	14.6	11
B. Follow-On Submissions				
SNDS- Total	2577	100	68.6	51.4
SNDS-FIC	1076	41.7	28.6	21.5
SNDS-Me Too	2514	97.6	66.8	50.0
SNDS-ER	1057	41.0	28.1	21.1
C. Total Brand Patents	3759		100	75.0
D. Total Brand Drugs	95			
E. Patents/Drug	39.6			
II. GENERIC SUBMISSIONS	1252	100		25
ANDS	744	59.4		
SANDS	508	40.5		
III. TOTAL (PATENTS)	5,011			100

Та	ble	7: N	lew	and	Foll	low-	On	Data	for	MP	Patent	Cohort

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Fig. 3b illustrates the results for patents relating to brand and generic approvals. Of drugs approved in the MP Approval Cohort, 75% of related patents were granted to brand drug companies (•; NDS and SNDS) and 25% to generic companies (•; ANDS and SANDS). The change in relation to the brand v. generic ratio generally tracks that for new v. follow-on patents in Fig. 3a. As with approval data, the number and fraction of total patents granted to generic firms are substantial. The presence of significant patenting activity the MP Patenting Cohort likely reflects the substantial number of brand drugs coming off patent protection over the course of the test period.



**Fig 3. Profile of Pharmaceutical Innovation between 2001-2008 for Most Profitable Patent Cohort**. *a* New v. follow-on patents. Of total patents associated with drugs approved over the test period, 24% constituted New Drug Submissions (•; NDS) while 76% were for "follow-on" drugs (•; SNDS, ANDS and SANDS). *b* Patents associated with Brand-name v. Generic approvals. Of all drugs approved during the test period, 75% of patents were granted to brand-name drug companies (•; NDS and SNDS) and 25% to generic companies (•; ANDS and SANDS). *c* Details of patents. 33% of patents were for NDS and SNDS "First in Class" (•; FIC) drugs while 65% were for NDS and SNDS "Me-Too" drugs (•). *d* Patents associated with Most Innovative drugs. While 20% of patents during the test period were directed to NDS New Active Substances (•; NAS), 11% of NDS patents were directed to FIC drugs, and 21% of NDS patents were associated with drugs approved under an

expedited review process (•; Priority Review and NOC/c), 11% of patents associated with drugs approved over the period 2001-2008 contained an NDS NAS, underwent some form of NDS ER and were directed to NDS FIC therapies (•). Areas are approximations of calculated means for the entire test period.

A more detailed analysis of new and follow-on approvals is provided in Fig. 3c. The data indicate that that 33% of approvals were for NDS and SNDS FIC drugs ( $\bigcirc$ ; FIC) while 65% were for NDS and SNDS Me-Too drugs ( $\bigcirc$ ). Comparing data in Figs. 2 and 3 and Tables 4 and 6, one observes that the fraction of combined NDS and SNDS Me Too drugs was identical in the MP Approval Cohort and MP Patenting Cohort. By contrast, the fraction of combined NDS patents associated with FIC drugs jumped from 16% in the MP Approval Cohort to 33% in the MP Patenting Cohort, an increase of close to 200%.

The differences are more pronounced when the distribution of patents within NDS and SNDS drug classes is analyzed. Here, we see that the percent NDS FIC patents is 47% of total NDS patents compared to 39% in the MP Approval Cohort. This represents a 21% increase in patenting activity above the fraction of approvals in the same class. SNDS FIC patents accounted for 42% of all SNDS patents compared to 15% of approvals accounting for all SNDS approvals in the MP Approval Cohort, representing a 180% increase in patenting activity above the fraction of approvals in the same SNDS FIC class. In contrast, NDS Me Too patents represent 63% of total NDS patents accounted for 98% of all SNDS patents compared to 85% of approvals accounting for all SNDS approvals in the MP Approval Cohort. SNDS Me Too patents accounting for all SNDS patents compared to 85% of approvals accounting for all SNDS approvals in the MP Approval Cohort. As with the MP Approval Cohort, shifts in normalized and raw data between cohorts are reviewed in more substantial detail in the Discussion.

The details of patenting activity relating to the most innovative drugs are provided in Fig. 3d. The data illustrate that while 20% of all patents associated with drugs approved in the MP Approval Cohort were directed to NDS New Active Substances (•; NAS), 11% of NDS patents were directed to FIC drugs, and 21% of NDS patents were associated with drugs approved under an expedited review process (•; Priority Review and NOC/c), a total of 11% of all patents associated with drugs approved in the MP Approval Cohort contained an NDS NAS, underwent some form of NDS ER and were directed to NDS FIC therapies (•). This represents a 2-fold increase in the fraction of indicator moving from the MP Approval Cohort to the MP Patent Cohort.

Compared to NDS MI data for the MP Approval Cohort, the increase in the fraction of NDS MI drugs in the MP Patent Cohort is a result of an across the board increase in NDS NAS, NDS ER, NDS FIC classes. The percentage

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increase in class values in the MP Patent Cohort compared to comparable values in the MP Approval Cohort are 82%, 65%, and 93% for NDS NAS, NDS ER, NDS FIC patents, respectively.

#### D. MP Chemical Cohort

Data for the MP Chemical Cohort and all classes of NDS, SNDS, ANDS, and SANDS approvals are provided in Fig. 4 and Table 8. As reviewed in greater detail below, an important observation is that the numerical trends in general and detailed class values observed between the Total Approval Cohort, MP Approval Cohort and the MP Patent Cohort continue to develop in the same direction in the MP Chemical Cohort.



**Fig 4. Profile of Pharmaceutical Innovation between 2001-2008 for Most Profitable Chemical Cohort.** *a* New v. follow-on chemicals. Of total drugs approved over the test period, 37% constituted New Drug Submissions (•; NDS) while 63% were for "follow-on" drugs (•; SNDS, ANDS and SANDS). *b* Brand-name v. Generic chemicals. Of all drugs approved during the test period, 86% of chemicals were granted to brand-name drug companies (•; NDS and SNDS) and 14% to generic companies (•; ANDS and SANDS). *c* Details of chemicals. Of, 33% were for NDS and SNDS "First in

Class" ( $\bigcirc$ ; FIC) drugs while 71% were for NDS and SNDS "Me-Too" drugs ( $\bigcirc$ ). *d* Most innovative chemicals. While 30% of chemicals during the test period were directed to NDS New Active Substances ( $\bigcirc$ ; NAS), 15% of NDS chemicals were directed to FIC drugs, and 33% of NDS submissions were approved under an expedited review process ( $\bigcirc$ ; Priority Review and NOC/c), 15% of all drugs approved over the period 2001-2008 contained an NDS NAS, underwent some form of NDS ER and were directed to NDS FIC therapies ( $\bigcirc$ ). Areas are approximations of calculated means for the entire test period.

TYPE OF APPROVAL		DRUG CHEMICALS						
	Chemicals (No.)	Percent Submission Type	Percent Brand	Percent Total				
I. BRAND SUBMISSIONS								
A. New Drug Submissions								
<ul> <li>NDS – Total</li> </ul>	48	100	42.8	36.9				
NDS-FIC	20	41.6	17.8	15.4				
NDS-Me Too	30	62.5	26.7	23.0				
NDS- NAS	39	81.3	34.8	30.0				
NDS-ER	43	89.6	38.4	33.0				
NDS- MI	20	41.7	17.8	15.4				
B. Follow-On Submissions								
SNDS- Total	64	100	57.2	49.2				
<ul> <li>SNDS-FIC</li> </ul>	24	37.5	21.4	18.5				
SNDS-Me Too	62	96.9	55.3	47.7				
<ul> <li>SNDS-ER</li> </ul>	26	40.6	23.2	20.0				
C. Total Brand Chemicals	112			86.1				
D. Total Brand Drugs	90							
E. Chemicals/Drug	1.24							
II. GENERIC SUBMISSIONS	18	100		13.9				
ANDS	13	72.2						
SANDS	5	27.8						
III. TOTAL (CHEMICALS)	130	13.8		100				

	Table 8: New and	Follow-On	Data for MP	<sup>9</sup> Chemical	Cohort
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The percentages of total chemicals associated with the MP Approval Cohort in new and follow-on drug classes is given in Fig. 4a. Of total chemicals associated with the most profitable drugs over the test period, 37% were affiliated with drugs approved via the new drugs pathway (•; NDS) while 63% were associated with "follow-on" drugs (•; SNDS, ANDS and SANDS). The percentage of indicator associated with new drugs increased from 24% in the MP Patent Cohort to 37% in the MP Chemical Cohort, while the fraction of indicator associated with follow-on drugs decreased from 76% in the MP Patent Cohort to 63% in the MP Chemical Cohort. This represents the second order of change from the 85:15 ratio observed in the Total Approval and MP Approval Cohorts.

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Fig. 4b shows chemical data associated with brand and generic approvals. Of drugs approved in the MP Approval Cohort, 86% of related chemicals were granted to brand drug companies ( $\bullet$ ; NDS and SNDS) while 14% were granted to generic companies ( $\bullet$ ; ANDS and SANDS). Compared to relevant values for the MP Patent Cohort, the fraction of chemicals associated with new drugs increased from 75% to 86% and the percent associated with follow-on drugs declined from 25% to 14%. While the number and fraction of total chemicals granted to generic firms is not insignificant, the lower value likely reflects the decreased need by generics for developing new chemical compounds to legally protect generic substitutes compared to approvals and patents.

Analysis of chemicals associated with new and follow-on FIC and Me Too approvals is provided in Fig. 4c. While 33% of chemicals were for NDS and SNDS FIC drugs (•; FIC) drugs, 71% were for NDS and SNDS Me-Too drugs (•). Comparing the percentage of NDS and SNDS patenting and chemical data in Figs. 3 and 4 and Tables 7 and 8, the fraction of Me Too and FIC chemicals in both NDS and SNDS classes were very similar to those for patents. There was a 10% decline in indicator value from NDS patents to NDS chemicals and no change going from NDS Me Too patents to NDS Me Too chemicals.

In contrast, the fraction of total indicators across all NDS, SNDS, ANDS and SANDS classes differed substantially. There was a 2-fold increase in the percentage of chemicals associated with NDS FIC drugs going from the MP Patent Cohort to the MP Chemical Cohort and a 27% increase going from SNDS FIC patents to chemicals. Similarly, there was a 2.3-fold increase chemicals associated with NDS Me Too drugs when expressed as a fraction of all chemicals in the MP Chemical Cohort compared to the MP Patent Cohort, and a 20% increase SNDS Me Too indicator values going from MP Patenting Cohort to the MP Chemical Cohort. Thus, the observed change in the distribution of chemicals in varying new and follow-on classes compared to that for patents depended strongly on how the data were normalized. This, along with the relevant importance of shifts in raw data between cohorts, is reviewed in more detail in the Discussion.

Fig. 4 provides data relating to chemicals associated with the most innovative drugs. As shown in Fig. 4d, while 15% of NDS patents were directed to FIC drugs, a substantial fraction of chemicals associated with the MP Approval Cohort during the test period was directed to either NDS New Active Substances (○; NAS; 30%) or drugs approved under an expedited review process (●; ER; 33%). The fraction of chemicals associated with drugs approved in the MP Approval Cohort that contained an NDS NAS, underwent

some form of NDS ER and were directed to NDS FIC therapies  $(\bigcirc)$  rose to 15% of total chemicals in the cohort.

Compared to the data for the MP Patent Cohort, the increase in the percentage of NDS MI chemicals was not a result of a uniform increase in NDS NAS, NDS ER, NDS FIC classes. Rather, the comparatively large increase in NDS MI value from 11% in the MP Patent Cohort to 15% in the MP Chemical Cohort was a result of a 50% increase in NDS NAS value combined with a 57% increase in NDS ER value. By comparison the NDS FIC value only rose by 36% in the MP Chemical Cohort. The distribution of indicator across NDS drug classes and the impact thereof on the NDS MI value for the MP Chemical Cohort is similar to that for MP Approval Cohort.



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Fig. 5. Summary and Comparison of Drug Approvals, Drug Patenting and Chemical Components in Total Approval, MP Approval, MP Patent and MP Chemical Cohorts. Spider graphs showing the number of approvals in the Total (*a*) and Most Profitable (*b*) approval cohorts, patents in the Most Profitable Patent Cohort (*c*) and chemicals in the MP Chemical Cohort (*d*). Data are normalized for peak values in each instance in order to increase separation. Maximal values for raw data are 1049, 228, 2577 and 64 in panels *a-d*, respectively. Each plot has an equal number of tics from zero to the maximal value. Indicator data are shown for 10 line extension (SNDS) and new (NDS) drug classes, including SNDS (S), SNDS Me Too (S<sub>MT</sub>), SNDS First in Class (S<sub>FIC</sub>), SNDS Expedited Review (S<sub>ER</sub>), NDS (N), NDS Me Too (N<sub>MT</sub>), NDS New Active Substance (N<sub>NAS</sub>), NDS First in Class (N<sub>FIC</sub>), NDS Expedited Review (NS<sub>ER</sub>) and NDS Most Innovative (N<sub>MI</sub>) drugs. For details of drug nomenclature see Methods.

Fig. 5 provides a comparative summary of all of the raw data analyzed in this study. Data are graphed in spider plot format, which allows large numbers of drug classes to be compared directly and simultaneously against one another both within a given cohort and across cohorts. In all four cohorts studied, the data had two broad "shoulders" at the top of the graph representing line extension (SNDS) and line extension Me Too (SNDS Me Too) drugs. A second repeating pattern was for a "tripod" component at the bottom of the radial plots, composed primarily of NDS, NDS NAS and NDS ER drugs.

Analysis of the Total and Most Profitable Approvals Cohorts yielded a similar but slightly different picture. As evidence by the shoulder components of both plots, the data are dominated in both approval cohorts by follow-on line extension drugs generally and follow-on Me Too drugs in particular. The major difference observed between the Total and MP Approval Cohorts is the reduction of drugs in the NDS Me Too class and the larger fraction of drugs in the NDS ER, NDS NAS, and SNDS ER classes. Thus, while the shoulders continued to represent the most substantial numbers of approvals in the SNDS and SNDS Me Too classes, the tripod broadened out due to the increased number of NDS NAS, NDS ER and SNDS ER drugs. The increase in drugs in the NDS ER and SNDS ER classes in Fig. 5b is not surprising in light of the fact that many of the most profitable drugs are targeted by regulators earlier in the product lifecycle as candidates for expedited review.

Data for the MP Patenting Cohort are provided in Fig. 5c. As observed in Figs. 1a and 1b *supra*, conventional line extension and line extension Me Too patents dominated the data set even though patent protection was assessed more narrowly only for the most profitable drugs rather than the entire approval cohort. This indicates that the most extensive patenting activity by brand firms is for line extension rather than new drugs, notwithstanding the fact that patenting is typically thought to be proportional to the degree of breakthrough innovation. Even so, continuing the trend from Total to MP Approvals, there was a general broadening of the core of the radial plot in Fig.

5c, corresponding to a more significant tripod component in the spider plot. As in the MP Approval Cohort, this included increases in patents for new drugs generally (NDS) and for NDS ER and NDS NAS drugs in particular; the main difference was a comparatively larger increase in NDS and NDS ER drugs for patenting compared to approvals. Thus, new drugs are subject to significant patenting activity compared to approvals *per se*.

Finally, Fig. 5d illustrates data for the MP Chemical Cohort. Data for chemicals were similar to those for patents. As can be seen clearly by the trend in the radial plot, both SNDS and SNDS Me Too chemicals dominated the data set while the core of the tripod area continued to widen compared to other cohorts described thus far. One of the biggest changes compared to other cohorts was the large increase in chemicals in the NDS category. This result broadened out the tripod area more symmetrically compared to the other cohorts. In addition, compared to data for the MP Patent Cohort, the increase in the percentage of NDS MI chemicals was not a result of an across the board increase in NDS NAS, NDS ER, and NDS FIC classes. Rather, the elevated NDS MI value for the MP Chemical Cohort was a result of a strong increase in chemicals associated with both NDS NAS and NDS ER drugs. In addition, NDS FIC drugs rose by nearly a third compared to the MP Patent Cohort.

#### E. Class Trends Across Indicators

Tables 9 and 10 provide data relating to general trends observed in various new and follow-on categories across the three indicators as well as detailed information pertaining to several classes of new and follow-on drugs across indicators. Table 9 provides general data relating to new and follow-on drugs in three approval groups we have studied over the last four years (the original 2009 Berkeley analysis, the updated 2010 Total Approval Cohort and the narrowed and updated to 2010 MP Approval Cohort). The lower portion of the table provides a more granular level of detail regarding the percentages of new and follow-on FIC and Me Too drugs in each of the three approval groups. Table 10 provides both general and more granular detail regarding new and follow-on FIC and Me Too drugs expressed in rank order format. The rank order data indicate which categories and classes of drugs represented the largest studied, the smallest studied, and the groups in between. The data are in Table 10 are parsed in two ways. First rank orders are provided only for NDS, SNDS and Generic categories of approvals, patenting and chemicals in the four cohorts studied. Second, rank orders are provided in relation to the manner in which approval, patenting and chemical data are distributed across ER, NAS, FIC and Me Too drug classes. The data in both tables are presented graphically
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in Figs. 6 and 7.

#### Table 9. Comparison of New and Follow-On Approvals Across Cohorts

DRUG TYPE*	MOST PROFITABLE (2011)	TOTAL UPDATED (2011)	TOTAL (2009)
I. GENERAL CATEGORY			
A . New	14.7%	14.9%	15.0%
B. Follow-On	85.3%	85.1%	85.0%
C. Cohort	347	2,087	2,112
II. SUB-CATEGORIES			
A. New • NDS FIC • NDS Me Too	5.7% 8.9%	3.1% 11.7%	3.1% 11.2%
B. Follow-On • SNDS FIC • SNDS Me Too	9.7% 55.9%	3.5% 46.8%	3.6% 47.0%

\*NEW: New Drug Submission; FOLLOW-ON: SNDS, ANDS and SANDS submissions; COHORT: Number of drugs in study Group; FIC: First in Class; %: Values expressed as a percentage of all drugs per Cohort (NDS, SNDS, ANDS and SANDS. Coherence between New and Follow On data sets across Cohorts validates using MP set for patent and chemical analysis. Note that the largest differences were in NDS and SNDS sub-categories, particularly regarding the distribution of drugs in the MP Too and First in Class (FIC) cohorts.

### Table 10: Comparison of Total and Brand Rank Orders Across Indicators

A. INDICATOR	RANK ORDER (TOTAL DATA)	
I. APPROVAL- TOTAL	SNDS > Generic > NDS	
II. APPROVAL- MOST PROFITABLE	SNDS >> Generic = NDS	
III. PATENTS- MOST PROFITABLE	SNDS >> Generic = NDS	
IV. CHEMICALS- MOST PROFITABLE	SNDS >> NDS > Generic	
B. INDICATOR	RANK ORDER (BRAND DATA)	
I. APPROVAL- TOTAL	SNDS Me Too >>> NDS Me Too > NDS NAS	
II. APPROVAL- MOST PROFITABLE	SNDS Me Too >>> SNDS ER = NDS ER = NDS NAS	
III. PATENTS- MOST PROFITABLE	SNDS Me Too >> SNDS FIC = SNDS ER = NDS ER	
IV. CHEMICALS- MOST PROFITABLE	SNDS Me Too >>> NDS ER > NDS NAS	

Table 9 demonstrates coherence in the percentage of new and follow-on drugs in the Total Approval Cohort as it was originally assessed in 2008, after being updated in 2010, and after the latter database was narrowed to a cohort of the most profitable drugs. As suggested by the data in the top portion of Table 9, there was no meaningful difference between the percentages of new (15%) and follow-on (85%) drug approvals in the three approval groups despite large differences in the number and type of approvals investigated (2,122, 2,087, v. 347 approvals; 608, 608, v. 95 marketed drugs; cohort of total drugs approved over a ten year period v. cohort of only the most profitable drugs approved over the same period).

However, as indicated by the data in the lower portion of the table, there was, however, a significant difference in the fraction of new and follow-on FIC and Me Too drugs that is absent when only new and follow-on categories generally are investigated. For example, the percentages of new and follow-on FIC drugs increased in the MP Approval Cohort by 83% and 177%, respectively. While both classes of FIC drugs were elevated compared to the Total Approval Cohort, the increase was much more substantial in the line extension category compared to the new drug category. In contrast, the percentage of NDS Me Too drugs in the MP Approval Cohort decreased by 25%, as one might expect in a group of highly profitable drugs. However, and contrary to this point, the fraction of follow-on SNDS Me Too drugs in the present study, even in the sub-group of drugs that are the most profitable. As noted below in the Discussion, this finding comports with sales data for SNDS Me Too drugs.



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**Fig 6. Comparison of Category and Class Rank Orders Across Indicators.** *a* Comparison of Total Approval Cohort (T-APP), MP Approval Cohort (MP-APP), MP Patent Cohort (MP-PAT) and MP Chemical Cohort (MP-CHEM) data across SNDS (filled bar), Generic (thatched bar), and NDS (open bar) categories. Note that SNDS category drugs represented the greatest fraction of all indicators across Cohorts, and that the rank order is SNDS > Generic > NDS for all Cohorts except the MP-CHEM Cohort. *b* More detailed comparison of T-APP, MP-APP, MP-PAT and MP-CHEM Cohort rank orders across specific drug classes. Data are shown for SNDS Me Too drugs (SNDS-MT), NDS Me Too drugs (NDS-MT), SNDS ER drugs (SNDS-ER), NDS ER drugs (NDS-ER), and NDS NAS drugs (NDS-NAS). Data show that the SNDS Me Too class was greatest across all four Cohorts, and that the fraction of drugs in SNDS-ER, NDS-ER and NDS-NAS classes increased across Cohorts.

As illustrated by the rank order data in Table 10A, SNDS data across the numerous new and follow-on categories were always greater (>) or much greater (>>) than data in the same class for NDS and Generic categories. This was true for all four cohorts. Somewhat surprisingly, the Generic group had a rank order that was either larger (Total Approval Cohort) or equal (MP Approval and Patenting Cohorts) than that observed for the NDS group. Only

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the MP Chemical Cohort had the NDS category in second rank. This can be appreciated visually in the spider graph in Fig. 5c, the bar graph in Fig. 6a, and the line graph in Fig 7a. The first of these shows a clear 'bump' in the radial data at the NDS datapoint (indicated "N" on the outside axis), whereas the latter two graphs both demonstrate a clear cross-over point in the MP Patent Cohort for NDS drugs compared to the trends for both approval cohorts. Fig. 6 illustrates that the 3 bars within each set decline uniformly by class to the effect that SNDS > Generic > NDS in the Total Approval, MP Approval, MP Patent Cohorts. In the MP Chemical Cohort, however, the NDS value jumps back up nearly to the level of the SNDS value. Fig. 6a illustrates this in a different but equally effective manner. Both the SNDS and Generic data points are essentially oscillating across indicators to varying degrees. The exception is the NDS group, which is increasing with indicator such that there is a significant cross-over point in between the MP Patent Cohort and the MP Chemical Cohort.



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**Fig 7. Comparison of Category and Class Rank Orders Across Indicators.** *a* Comparison of Total Approval Cohort (T-APP), MP Approval Cohort (MP-APP), MP Patent Cohort (MP-PAT) and MP Chemical Cohort (MP-CHEM) data across SNDS (filled bar), Generic (thatched bar), and NDS (open bar) categories. Data are the same as in the previous figure only with line graphs to show the cross-over of NDS data at the MP-PAT Cohort. *b* More detailed comparison of T-APP, MP-APP, MP-PAT and MP-CHEM Cohort rank orders across specific drug classes. Data are shown for SNDS Me Too drugs (SNDS-MT), NDS Me Too drugs (NDS-MT), SNDS ER drugs (SNDS-ER), NDS ER drugs (NDS-ER), and NDS NAS drugs (NDS-NAS). Again, data are the same as in the previous figure except in line graph format to illustrate the rise in SNDS-ER, NDS-ER and NDS-NAS classes across Cohorts.

Table 10B and Figs 6b and 7b present analogous data for new and follow-on classes. The primary finding is that SNDS Me Too approvals, patents, and chemicals dominate the rank orders across indicators. The degree to which SNDS Me Too data dominate can be appreciated visually in Fig 6a, which demonstrates a 2-8 fold increase in SNDS Me Too beyond that of the closest rival class, the NDS Me Too class. This difference is observed across all indicators, as illustrated by the parallel drop in all four cohorts from the SNDS Me Too data to the NDS Me Too data.

The second, third and fourth ranked classes varied over the four Total Approval, MP Approval, MP patent, and MP Chemical Cohorts. This is illustrated for the rank orders in Section B of Table 10 and graphically in Fig. 6b and Fig. 7b. The jockeying for the mid-to-lower places within the rank order typically involved drugs in the middle to high range of innovative compounds such as SNDS ER and NDS ER, followed by NDS NAS, with SNDS FIC displacing both ER categories to the next rank below SNDS Me Too. There was one exception where the SNDS FIC indicator value displaced the SNDS ER and NSD ER classes in second place. Fig. 6b and Fig. 7b both illustrate that despite the apparent complexity of this distribution, the largest percent total class is always SNDS Me Too indicator, with the greatest gap between it and another class represented by the NDS Me Too class. However, in each of the four cohorts studied, the grouping of bars representing SNDS ER, NDS ER, and NDS NASs, all climb together upwards from a nadir in the Total Approval Cohort to progressively greater values in the MP Approval. Patenting and Chemical Cohorts. The differences among the four cohorts are clearly evident in the graph provided in Fig 7b.

#### V. DISCUSSION

The purpose of this study was to develop a harmonized method to collect, compare and quantify regulatory approval, patenting and chemical compound data from multiple cohorts of new and follow-on drugs. Drug classes were chosen to encompass those typically described and prioritized by domestic drug regulators in developed nations. A related goal was to go beyond

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simplified descriptors of new and follow-on drugs often found in the literature, and to categorize the various classes of new, line extension and generic approvals according to the detailed nomenclature used by regulators themselves. In total, 2,087 drug approvals, 5,011 patents and 130 chemical components were analyzed. The first major observation was that by far the greatest fraction of all indicators studied was in the Me Too class. More specifically, the vast majority of approval, drug patenting and chemical indicators was associated with line extension (SNDS) Me Too drugs. The second largest class encompassed Me Too drugs approved via the new drug approval (NDS) route. Therefore, a major finding in this study is that the majority of all drug approvals, drug patents, and related chemical components developed by pharmaceutical companies are in relation to Me Too drugs. The second trend in the data is in relation to drugs in classes other than the Me Too class. Here we observed a growing trend as one moved from approvals, to patenting and then chemical components for an increasing fraction of indicator to be associated with drugs going through some form of expedited review (ER) or drugs that were deemed to contain a New Active Substance (NAS). Thus, while brand firms are putting most of their effort into developing Me Too drugs, new drugs moving through ER and new drug forms containing an NAS are also the subject of significant drug development activity. Third, the percentage of approvals, patents and chemicals deemed in the present study to be most innovative (NDS MI) was limited for each indicator by low numbers in the First in Class (FIC) designation, especially for new drugs. This result suggests that a focus on drugs in the NDS FIC class would be an excellent way for brand firms to increase the level of innovation in their pipelines in accordance with targets set by regulators. For this reason, NDS FIC drugs may also present a rational evidence-based target for enhanced or otherwise customized patent and regulatory rights layering. The fourth trend was the observation that, using the NDS MI classification to assess the degree of innovation, the level of apparent innovation increased steadily as one moved from drug approvals to drug patents and then chemical components. This result suggests that the functional utility of indicators for drug development expressed as a rank order is chemicals > patents > approvals. This rank order will differ, however, when parsed through the lens of patent law working in conjunction with linkage law, as only drug approvals and drug patents are linked via pharmaceutical linkage and even then patent rights are secondary to marketing license rights. Finally, surprisingly large numbers of generic approvals, patents and chemical indicators were observed. Not only were the number and fraction of indicators large, but generic indicators often exceeded those in the new drug approval route for brand firms. This result suggests that a

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large percentage of brand drugs came off patent protection over the course of the study, and that generic firms may be accruing a greater number of approvals, patents and chemical components than may have been previously recognized. The data obtained support the conclusion that generic firms are following the lead of their sister brand firms by creating substantial clusters of products and patents over time.

### A. Interpretation of Data

#### 1. Drug Approval

As indicated by the data shown in the various Tables and Figures in this Article, the vast majority of brand drug approvals are for follow-on drugs. For both the Total Approval and MP Approval Cohorts, the split was 85% follow-on drugs and 15% new drugs. While the overall percentages of new and follow-on drugs for the Total and Most Profitable Cohorts were in general quite similar, the distribution of drugs within new and follow-on classes did at times differ significantly (cf. Figs. 1, 2 and 5; Tables 9 and 10).

As noted in the literature, it is a hotly contested issue whether follow-on drugs represent an important aspect of innovation in the pharmaceutical sector.<sup>69</sup> Me Too drugs have come under particular scrutiny, as this class of drugs often offer a similar risk: benefit profile to drugs that are already on the market, including drugs in generic form. Our data illustrate that the majority of drugs approved by regulators are line extensions of drugs already on market, even in the more narrowly defined MP Approval Cohort. For example, in both the Total and MP Approval Cohorts a substantial majority of drugs approved were SNDS Me Too drugs, followed by NDS Me Too drugs. For the Total Approval Cohort, 79% of all NDS approvals were for NDS Me Too drugs

<sup>&</sup>lt;sup>69</sup> See, e.g., CHANGING PATTERNS, supra note 40, at 2-8; John Abraham & Courtney Davis, A Comparative Analysis of Drug Safety Withdrawals in the UK and the US (1971–1992): Implications for Current Regulatory Thinking and Policy, 61 SOC. SCI. & MED. 881 (2005); DiMasi & Faden, supra note 11 at 23; Drugs in 2001, supra note 10; Domenico Motola et al., An Update on the First Decade of the European Centralized Procedure: How Many Innovative Drugs?, 62 BRIT. J. OF CLINICAL PHARMACOLOGY 610, 614 (2006); Editorial, European and French Pharmaceutical Market Assessed by Prescrire in 2005: Mainly Bogus Innovation, 30 FARMACIAHOSPITALARIA 68 (2006) [hereinafter Editorial]; Kenneth I. Kaitin et al., Therapeutic Ratings and End-of-Phase II Conferences: Initiatives To Accelerate the Availability of Important New Drugs, 31 J. CLINICAL PHARMACOLOGY 17 (1991); New Medicines in 2007: Regulatory Agencies and Policy Makers Leave Public Health in the Hands of the Pharmaceutical Industry, 17 PRESCRIRE INT'L 78 (2008) [hereinafter New Medicines in 2007].

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while 93% of all SNDS approvals were for Me Too drugs. This decreased slightly to 76% and 85% for NDS and SNDS approvals in the MP Approval Cohort. In terms of raw approvals, there were a total of 245 and 976 Me Too drugs in the NDS and SNDS categories in the Total Approval Cohort. This represents a remarkable 400% increase in the number of line extension Me Too drugs compared to new Me Too drugs. The same pattern was observed in the MP Approval Cohort; there were 31 and 194 Me Too drugs in the NDS and SNDS categories, representing a 530% greater number of follow-on Me Too drugs compared to new Me Too drugs. These trends are reflected by the broad "shoulder" components of the spider graphs in Figs. 5a-5b. The data reported here are consistent with the observation in our earlier McGill study that SNDS Me Too approvals increased exponentially over time, i.e., non-linearly, between 2001 and 2008.<sup>70</sup>

Compared to the Total Approval Cohort, the drugs in the Most Profitable Approval Cohort received very large numbers of approvals for SNDS and NDS drugs undergoing some type of Expedited Review (Priority Review or NOC/c). For the Total Cohort, 15% of all NDS approvals were for NDS ER drugs. This number increased a remarkable 5.7 times to 86% of all NDS approvals in the MP Cohort. The absolute numbers declined for SNDS approvals, which were 5% and 20% for SNDS approvals in the Total and MP Cohorts, respectively. However, the increase from Total Approval to MP Approval Cohort remained high (3.8 times). Even so, the raw numbers between Approval Cohorts were not substantially different. There were 47 and 44 NDS ER drugs in the Total and MP Approval Cohorts, respectively, and 56 and 46 SNDS ER drugs in the Total and MP Approval Cohorts, respectively.

The difference in the numbers of Me Too approvals expressed as a percent of brand approvals and raw numbers is a function of three variables. The first is the much larger sample size for the Total (n=2,087) compared to the MP (n=95) Approval Cohorts. The second is the fact that the MP Approval Cohort includes *only* drugs that have already been vetted by the market to be Most Profitable, while the Total Approval Cohort is for all drugs approved during the test period. Finally, and perhaps most importantly, the raw numbers reveal the extent to which the Me Too numbers dominate both classes, representing the vast majority (76-93%) of brand drugs approved per category.

As noted at the outset of the Methods, drugs containing a NAS (parallel to the NCE designation in other jurisdictions) and drugs designated as FIC are considered to be hallmarks of innovation in the pharmaceutical sector. For the Total Cohort, only a very small number (3%) of all NDS approvals were for

<sup>&</sup>lt;sup>70</sup> Sawicka & Bouchard, *supra* note 29, at 100, Figure 8.

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NDS FIC drugs. This increased by 2-fold to 6% NDS FIC drugs in the MP Approval Cohort. Similarly, while 3.5% of all approvals in the Total Approval Cohort were for SNDS FIC drugs, this number increased 2.8-fold to 9.7% for SNDS FIC drugs in the MP Approval Cohort. Regarding the raw numbers between Cohorts, there were 65 and 20 for NDS ER drugs in the Total and MP Approval Cohorts and 73 and 34 SNDS ER drugs in the Total Approval and MP Approval Cohorts. This represented a decrease of 3.25 times and 2.15 times the numbers of approvals in the NDS FIC and SNDS FIC groups, respectively.

The last group to demonstrate a significant change was NDS NAS drugs. This value increased 1.8-fold from 42% of brand submissions in the Total Cohort to 76% in the MP Cohort. The raw data values were 130 and 39 NDS NAS drugs in the Total and MP Cohorts, respectively, essentially tracking the decreased Cohort size. When analysed as a fraction of total approvals, however, the values were lower. The percentage of total approvals in the Total Approval Cohort and MP Approval Cohort were 6.2% and 11.2% of all approvals, respectively. A comparison of the same normalized values in the Total Approval Cohort indicates that the percentage of NDS submissions directed to NAS compounds nearly doubled, from 42% in the Total Approval Cohort to 76% in the MP Approval Cohort. This, along with the comparable increases in the fraction of NDS ER and NDS FIC drugs, is the main reason why the NDS MI values increased almost 500% in the most profitable group.

The most innovative drugs were quantified and these values are represented graphically in Fig. 1d and Fig. 2d for the Total Approval and MP Approval Cohorts, respectively. As previously reported,<sup>71</sup> the number and percentage of NDS MI approvals for the Total Approval Cohort is very small, amounting to just 22 of 2,087 approvals, or 1.1% and 1.6% of all total and brand approvals. Not surprisingly, this value increased significantly in the MP Approval Cohort. While the percentage values for NDS NAS (15%), NDS FIC (5.7%) are similar to those observed for the Total Approval Cohort, data for NDS ER (12.7%) and NDS NAS (11.2%) are higher in the MP Approval Cohort, particularly when expressed as a function of only NDS submissions (86% and 76%). The result is that the value for NDS MI approvals is over 5-fold higher (5.7%) in the MP Approval Cohort compared to the Total Approval Cohort, which shows up as a small bump in the NDS MI data in the spider graph compared to other drug classes (Fig. 5b). This increase was observed even though the actual number of NDS MI drugs decreased from 22 to 20, reflecting the strong increase in NDS MI drugs in drugs that are the most profitable in the much

<sup>&</sup>lt;sup>71</sup> Bouchard 2009, *supra* note 9, at 1492-93.

smaller cohort.

The results in this Article raise the possibility that the "rational ignorance" suggested to exist at the Patent Office<sup>72</sup> may also extend to drug regulators as well. Evidence for this includes the substantial majority of drugs approved by regulators that are follow-on in nature, the fact that of these the vast majority are line extension drugs generally and line extension Me Too drugs (SNDS Me Too) specifically, the observation that the next largest class next to line extension drugs is Me Too drugs approved via the new drug approval route (NDS Me Too drugs), and the wide-spread criticisms of the potential harms of a regulatory preference for Me Too drugs on both public health and the capacity of drug companies to produce pioneering drugs. Further evidence favouring some form of rational ignorance is the rank order of apparent utility of chemicals > patents > approvals, as well as the likely possibility that relatively low standards of approval for various new and follow-on drugs (e.g., NDS NAS and SNDS classes) conduces to a cluster-based drug development strategy that delays generic entry on older blockbuster drugs. It would be valuable to know whether drug regulators approve almost all of the applications they process as apparently occurs with patent examiners,<sup>73</sup> with a parallel conclusion that domestic drug regulation may similarly represent an "unwieldy mechanism" with which to support national productivity.<sup>74</sup> In the case of regulatory approvals, productivity would equate to the public health benefits associated with a regulatory and economic preference for follow-on drugs.

Finally, it is noteworthy that there are substantial numbers of drug approvals granted to generic firms. Indeed, the scope of approvals for generics may represent a higher value than previously recognized. Remarkably, the number of generic approvals often exceeded those for NDS drugs. In the Total Approval Cohort, generic approvals accounted for 35% of all drug approvals, representing 727 of 2,087 approvals. Of these, 580, or 80% were for "new" abbreviated submissions (ANDS) while the remaining 20% were for "follow-on" generic submissions (SANDS). Thus, the number of both initial and follow-on generic approvals, accounting for 20% of total approvals in this group. These data reflect the fact that a significant proportion of brand drugs were genericized over the eight year test period. Of these, 84%, or 11

<sup>&</sup>lt;sup>72</sup> Lemley, *supra* note 4, at 1497; Cecil D. Quillen, Jr. & Ogden H. Webster, *Continuing Patent Applications and Performance of the U.S. Patent and Trademark Office*, 11 FED. CIR. B.J. 1, 3 (2001).

<sup>&</sup>lt;sup>73</sup> Quillen & Webster, *supra* note 72.

<sup>&</sup>lt;sup>74</sup> Parchomovsky & Wagner, *supra* note 4, at 24.

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approvals, were granted for follow-on generics, suggesting the speed of development of generic drugs over time is not insubstantial. Thus, both brand and generic drug firms appear to be following the same strategy for drug development. That is, the product cluster model.<sup>75</sup>

#### 2. Drug Patenting

As with approvals, the vast majority of brand patents are for follow-on drugs (Fig. 2, 5, 6 and 7; Tables 7 and 10). For the MP Patent Cohort, the split was 76% follow-on drugs and 24% new drugs. While the percentage of new and follow-on patents was in general similar to that for the MP Approval Cohort, the distribution of patents within classes differed significantly. The rank order for patenting was SNDS Me Too > SNDS FIC = SNDS ER = NDS ER. This was similar to that observed for the MP Approval Cohort, with the exception that both NDS and SNDS ER patents were displaced by SNDS FIC patents.

Most importantly, in both NDS and SNDS Cohorts a substantial majority of patents were for Me Too drugs. For the NDS Me Too Drugs, 63% of all NDS patents were for NDS Me Too patents while 98% of all SNDS patents were for Me Too drugs, representing a 1.6-fold increase from new to follow-on Me Too approvals. The raw numbers are even more remarkable. There were 742 and 2,514 NDS and SNDS Me Too patents, representing a 340% increase from new to follow-on Me Too patents. In other words, of all Me Too patents, 77% were for line extension, or SNDS, drugs. Combined, this represents 87% of all brand patents on the 95 drugs in the MP Cohort. Analogous to approvals in the MP Approval Cohort, patenting data within the MP Patent Cohort suggest that there is much greater competition within brand firms for SNDS Me Too patents.

Following SNDS Me Too patents, three sub-categories of patents came in a close second, third and fourth. These were SNDS FIC (n=1076), SNDS ER (1057) and NDS ER (1049). While NDS and SNDS ER patents were displaced by SNDS FIC patents compared to MP Cohort approval data, the data in Table 7 reveal it was not by much. As a result, the two categories of ER patents constituted a substantial fraction (56%) of all patents granted to brand firms. This can be contrasted to the 26% of all approvals in the MP Approval Cohort accounted for by the combination of NDS ER and SNDS ER approvals. Thus, there was twice the activity in the patenting cohort than in the approval cohort

<sup>&</sup>lt;sup>75</sup> Bouchard 2010, *supra* note 14, at 217. For a general description of product and patent portfolios, see, e.g., William Kingston, *Intellectual Property's Problems: How Far is the U.S. Constitution to Blame?*, 4 INT. PROP. Q. 315 (2002); PParchomovky & Wagner, *supra* note 4; EUROPEAN COMM'N PHARM. SECTOR INQUIRY, FINAL REP. (EC) July 9, 2009.

for ER indicators. While NOC/c and PR pathways in the ER class have similar evidentiary requirements,<sup>76</sup> both differ substantially from all other approval pathways in the degrees to which they meet unmet medical need identified by regulators.

The ER patenting data can be contrasted to data for FIC drugs, which require either changes to chemical form alone compared to drugs already approved (NDS) or in conjunction with a new use (SNDS). Thus, compared with the ER pathway, FIC drugs often involve more of a focus on chemistry as opposed to changes in benefit:risk and/or unmet medical need. Thus it is not surprising that the increase in SNDS FIC patenting is paralleled by increased number of patents in the NDS NAS class, which went from 42% of NDS brand approvals in the Total Approval Cohort to 76% in the MP Approval Cohort.

As noted below, the increased emphasis by brand firms on FIC and ER classes across indicators is likely related to the fact that regulators have vetted these candidates earlier in the product lifecycle than for the Total Approval Cohort. This is noteworthy, as both NOC/c and Priority Review approvals have faster and/or less onerous evidentiary processes compared to other drugs.<sup>77</sup> This is especially so for SNDS ER drugs, which increased by 400% in the MP Cohort.

Of note in the context of the emphasis by brand firms on follow-on ER and FIC patents, is the observations that FIC patents in the new drug category (NDS FIC) comprised the lowest value of all new drug classes save for the NDS MI category. NDS FIC patents accounted for 46.5% of total NDS brand patenting activity compared to 63% NDS Me Too, 84% NDS NAS and 89% NDS ER patenting activity. This number drops to 15% and then to 11% of all brand and total patents, respectively in the MP Patenting Cohort. The normalized values track the differences in raw data, as there were 500 patents directed to new FIC drugs while there were 1076 patents directed to follow-on FIC drugs. Thus, the data indicate a two-fold increase in the emphasis by brand firms on patents associated with follow-on FIC drugs as opposed to patents on new FIC drugs.

The drop in NDS FIC patents compared to SNDS FIC patents is slightly unusual in that follow-on FIC drugs require not only a new chemical form but also a new use. The likely explanation is that a NDS FIC drug represents the first drug in its chemical class and therefore has no comparator. By contrast, the new chemical form for SNDS FIC drugs is in accordance with the lower SNDS chemistry standard, and thus a SNDS FIC drug is a line extension rather

<sup>&</sup>lt;sup>76</sup> Bouchard & Sawicka, *supra* note 12, at 58-59.

<sup>&</sup>lt;sup>77</sup> Id.

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than a true first in class drug.

Judging patents according to the method employed for Fig 1., NDS NAS patents accounted for 20% total brand patenting, NDS FIC for 11%, NDS ER for 21% and patents on drugs that were approved via the NDS pathway and also contained an NAS, were directed to a FIC therapy, and underwent some type of ER, amounted to 550 (11%) of 5,011 patents. This is illustrated graphically in Fig. 3. The values for NDS NAS, NDS ER, NDS NAS, and NDS FIC patenting in the MP Patent Cohort were all significantly higher than corresponding values in the MP Approval Cohort. This rendered the fraction of NDS MI patents (11%). As with the Approval and Chemical data, the percent of NDS MI patents was limited by comparatively lower values in the NDS FIC class.

Finally, there was a significant number of generic patents in the MP Patenting Cohort. There were 744 and 508 patents in the ANDS and SANDS classes, respectively. Somewhat surprisingly, the fraction of patents in the MP Patent Cohort granted to generic firms (25%) was larger than the fraction of approvals to generics in the MP Approval Cohort (20%). Moreover, a much larger fraction of generic patenting was directed to "follow-on" (SANDS) patents (41%) than to "follow-on" generic approvals (16%). Thus, as with the approval data, the patent data suggest that generic firms are following the lead of their brand counterparts, assembling strong portfolios of approvals and patents for competitive reasons.

#### 3. Drug Chemical Components

As with data in the MP Approval Cohort and MP Patent Cohort, the general observation that vast majority of brand chemicals are for follow-on drugs (73% combined SNDS and Generic) is maintained in the MP Chemical Cohort (Figs. 4-7; Tables 8-10).

However, even with the general rank order, the chemical Cohort was different than the MP Approval and MP Patent Cohorts. While the percentage of total chemicals in the SNDS category (50%) was similar to that for patents (51%), the percentage of NDS chemicals (37%) was greater than that for patents (24%). In addition, the percentage of chemicals in the generic class (14%) was significantly reduced compared to the fraction of generic patents (25%). Moreover, as indicated by the rank order data in Table 8, the MP Chemical Cohort was the only cohort where the NDS class solidly occupied the second rank order ahead of the generic class. This result is shown graphically in Figs. 6 and 7. In Fig. 6, the trend is clearly downward for all SNDS, generic and NDS classes across the Total Approval, MP Approval and

Patent Cohorts. Only in the Chemical Cohort does the NDS value jump back upward nearly to the SNDS level. This result is even more evident in the trend lines in Fig. 6a. This graph evidences a clear cross-over point between Generic and NDS values at the MP Patent Cohort, and the NDS value reaches its maximum at the MP Chemical Cohort. Thus, while there are general trends that are harmonious from one indicator to the next (see below), the chemical data differ significantly from the patenting and approval data among the most profitable drugs.

Regarding brand rank orders specifically, once again the large majority of chemicals related to approvals for the MP Approval Cohort were SNDS Me Too drugs. Of the 112 brand chemicals, a remarkable 62 were directed to line extension Me Too drugs. However, as with the general rank order data, there were significant differences in the brand rank orders. This is illustrated by the data in Table 8 and particularly Table 10. While the SNDS Me Too category was the greatest at 55% of all brand chemicals, this was followed by two NDS categories, NDS ER and NDS NAS drugs. NDS ER drugs had 43 chemicals, accounting for 90% and 38% of NDS and total brand chemicals. The data for NDS NAS chemicals were very similar; 39 chemicals accounting for 81% and 35% of NDS and total brand chemicals. This result is similar in general to the rank orders for brand approvals and patents, which had a much greater emphasis on both NDS and SNDS ER drugs as well as NDS NAS drugs. Thus, while Me Too line extensions are associated with the greatest number of chemical compounds, firms also appear to be targeting their chemical development efforts towards the development of new drugs meeting unmet medical needs identified by regulators, particularly in the ER classes.

While brand firms appear to be targeting more of their effort in developing chemicals for NDS drugs compared to comparable data in the MP Patent, and especially MP Approval, Cohorts, a more detailed analysis reveals the substantial dominance of the SNDS Me Too category for chemical compounds. This category represented 97% of all brand SNDS chemicals and 55% of brand chemicals in all categories (Table 8). In comparison, NDS Me Too chemicals were 65% of brand NDS chemicals and only 27% of total brand chemicals. This difference also shows up when the raw data are assessed, with 62 chemicals in the SNDS Me Too category compared to 30 in the NDS Me Too category. The dominance of SNDS Me Too values present the largest fraction of total across all four Total Approval, MP Approval, MP Patents and MP Chemical indicators. Thus, as with the MP Approval and MP Patent Cohorts, there appears to be significantly greater competition within brand firms (SNDS) than between firms (NDS) for development of chemicals in relation to

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Me Too drugs.

Of interest is the observation that, like the data for MP Approval and MP Patent Cohorts, SNDS FIC drugs did not encompass a substantial fraction of chemical compounds expressed either as SNDS or total brand values. This class represented 38% of SNDS chemicals and 27% of all brand chemicals. Analysis of the raw data show of the 112 brand chemicals, 24 were directed to SNDS FIC drugs compared to 62 for SNDS Me Too drugs. In comparison, there were 2514 SNDS Me Too patents compared to 1076 SNDS FIC patents (43%). The patents accounted for 42% and 29% of SNDS and total brand patents, respectively. Similarly, there were 194 SNDS Me Too approvals compared to 34 SNDS FIC approvals (18%). These approvals accounted for only 15% and 12% of SNDS and total brand approvals, respectively. The data suggest that in the line extension category, brand firms are expending considerably more effort developing chemicals, patents and approvals in the Me Too category rather than the more innovative FIC category.

Judging chemicals according to the method employed for Fig 1, NDS NAS chemicals accounted for 30% total brand chemicals, NDS FIC for 15%, and NDS ER for 33% (Fig 4). Chemicals associated with drugs that were approved via the NDS pathway and also contained an NAS, were directed to a FIC therapy, and underwent some type of ER, amounted to 20 of 130 chemicals (15%). As with patenting, the values for NDS NAS, NDS ER, NDS NAS, and NDS FIC chemicals were all significantly higher than MP approval values, rendering the fraction of NDS MI chemicals (15%) higher than those in the MP Patent Cohort (5.7%), the Total Approval Cohort (1.1%), and the MP Patenting Cohort (11%). A related and important observation is that even more substantially than for the MP Patenting Cohort, the percent of NDS MI chemicals (15%) in the MP Chemical Cohort was limited by significantly lower values in the NDS FIC class (11%) compared with NDS NAS (30%) and NDS ER (33%) classes.

Finally, generic chemicals accounted for the smallest fraction of all indicators studied. Generics totalled 18 of 130 chemicals. This amounted to only 14% of total chemicals in the MP Chemical Cohort. Of these, 13, or 72% were in relation to ANDS approvals with the remaining 28% in relation to "follow-on" of SANDS approvals. The value of 14% is relatively low compared to comparable generic percentages of corresponding MP Patenting (25%), MP Approval (20%) and Total Approval (20%) Cohorts. That this is so seems reasonable given that generic firms are less oriented to developing "new" or otherwise useful chemicals needed to manufacture or otherwise protect generic drugs. The fact that generic chemicals account for as much as 15% of total chemicals in the cohort is nevertheless impressive given the

"copycat" nature of these products.

#### 4. General Trends Across Indicators

There are several general trends in the data across classes and indicators that are worth revisiting. The first is that the greatest fraction of all indicators is in the Me Too approval class. This can be seen by the dominance of the "shoulder" component across cohorts in the spider graphs in Fig. 5. As a result, a primary finding in this study is that the vast majority of all approvals granted by drug regulators, patents granted by the patent office, and chemicals developed by pharmaceutical companies are in relation to Me Too drugs. Calculated as a percentage of total brand indicators this amounts to a whopping 89% of all drug approvals in the Total Approval Cohort, 81% of all approvals in the MP Approval Cohort, 94% of patenting in the MP Patent Cohort, and 82% of chemicals in the MP Chemical Cohort. Based on the data reported in this Article, there is little question as to which drug class multi-national drug companies are targeting in their drug development activities. Indeed, of the top 25 most profitable drugs, 12, or 48%, were SNDS Me Too drugs.<sup>78</sup> In 2006 alone, these drugs had combined sales of US \$45.7 billion dollars.<sup>79</sup>

The second trend in the data is towards a growing percent total for SNDS ER, NDS ER and NDS NAS drugs across indicators. This trend can be seen in the gradual broadening of the "tripod" component across indicators in Fig. 5 and in Fig. 6b as a clear increase in the slope of representative class values across all four cohorts. This trend is also reflected in the changing dominance of follow-on Me Too indicators across classes. Within the three MP Cohorts specifically, there was a slow but steady decline in the fraction of total Me Too indicator that was in the line extension or SNDS class. This declined from 86% of all Me Too approvals in the MP Approval Cohort to 71% of Me Too patents in the MP Patent Cohort to 67% of Me Too chemicals in the MP Chemical Cohort.

Combined, these data suggest that as one moves, including within the MP data set itself, from approval to patenting to chemical data, there is an increasing incidence of brand firms focusing on classes other than SNDS Me

<sup>&</sup>lt;sup>78</sup> The ranks of these drugs were: 2 Advair (fluticasone + salmetrerol); 3 Plavix (clopidogrel); 5 Norvasc (amlodipine); 14 Protonix (pantoprazole); 16 Seroquel (quetiapine); 17 Prevacid (lansoprazole); 19 Cozaar (losartan); 20 Fosamax (alendronate); 22 Lovenox (enoxaparin); 23 Avandia (rosiglitazone); 24 Actos (pioglitazone); 25 Zocor (simvastin).

<sup>&</sup>lt;sup>79</sup> Andrew Humphreys, *MedAdNews* 200 – World's Best-Selling Medicines, MEDADNEWS, July 2007.

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Too drugs. As illustrated in Fig. 6b, the two most noticeable examples of this reversal are for NDS ER and NDS NAS drugs in the MP Chemical and MP Patenting indicators. This data indicate that even though brand firms are focusing their efforts on line extensions, significant levels of approvals, patenting and chemical development in the new drug category are also occurring.

The third general trend is that the percent of most innovative drugs in all four cohorts was limited by the comparatively lower number of NDS FIC values. It is not surprising that this class limits the innovation value for all indicators, as First in Class drugs are drugs that consist of either a brand new family of active ingredient(s) or old active ingredient(s) used for the treatment of a new indication. Therefore, a drug is deemed to be First in Class only where there is no other drug on the market that belongs to the same compound family and is used for the same indication e.g., where there is no comparator.

The scenario for the NDS FIC class differs substantially from other pathways for approval involving chemical or use changes. For example, SNDS status can be achieved by a wide array of chemical modifications, including alterations to the route of administration (oral to intravenous), dosage form (tablet to capsule), salt form (besylate to mesylate), crystalline form (monohydrate to dihydrate), etc. Similarly, NDS NAS status is achieved a chemical or biological substance not previously approved for sale as a drug or an isomer, derivative, or salt of a chemical substance previously approved for sale as a drug but differing in properties with regard to safety and efficacy.

The differing degrees of difficulty for the various new and follow-on classes show up in the raw data, where there were 20 chemicals in the NDS FIC group, 24 in the SNDS FIC group, 30 in the NDS NAS group, and 64 in the SNDS groups. Based on the wide array of chemical modifications that satisfy the SNDS and NAS requirements, we would expect to see the highest values for these groups, and indeed we do. We would also expect to see lower values with SNDS FIC drugs, as drugs in this class must have a new chemical form and a new use (Table 2). The observation that the NDS FIC class has the lowest number of chemicals is paralleled in the patent data (Table 7). It is also consistent with our earlier observation<sup>80</sup> that chemical patent classes in the MP Approval Cohort have the lowest rank order of all general patent classifications studied. Chemical patents, including patents directed specifically to crystals, chemical derivatives, enantiomers and salts made up only 12% of total classifications, with the remainder of the cohort composed of combination therapy (36%), use (15%), route of administration (24%), and process (13%)

<sup>&</sup>lt;sup>80</sup> Bouchard 2010, *supra* note 14, at 219.

patents. The data suggest that if firms wish to enhance the innovative value across all approval, patent and chemical indicators it would be via a focus on the NDS FIC class.

Even so, it appears from the data that the more profitable drug development pathway is via follow-on FIC drugs as opposed to new FIC drugs. This corresponds with the focus of brand firms on follow-on Me Too drugs, as both are classes of line extensions. As noted above, the follow-on Me Too class represented approximately 50% of the top 25 selling drugs and accounted for US \$45.7 billion dollars in 2006. In comparison, follow-on FIC drugs.<sup>81</sup> Profit on this group of drugs was US \$39.7 billion dollars in 2006. Combined, follow-on Me Too and follow-on FIC drugs accounted for 19 of the top 25 most profitable drugs, for a total of US \$85,470,000 in sales in a single year.

The fourth general trend was the observation that, using the NDS MI classification system to assess the degree of innovation, there was a strong trend towards increasing levels of innovation as one moved from drug approvals to drug patents and finally to chemical components. The NDS MI values increased steadily from the Total Approval Cohort (1.1%) to MP Approval Cohort (5.3%) to the MP Patenting Cohort (11%) and finally the MP Chemical Cohort (15%). Similar increases were seen in the combined NDS and SNDS FIC and ER values and NDS NAS values (Tables 5-8; Figs. 1-4). As noted *supra*, the NDS FIC group represented the lowest common denominator across indicators and dropped the NDS MI value accordingly in each of the four cohorts.

Based on the NDS MI values, as well as NDS and SNDS ER and NAS values, the data suggest that the "utility" of indicators reported here with regard to drug development may be highest for chemical components, lowest for approvals, with patents occupying the middle ground. Even so, only the latter two provide legal license to market drug products and so require heavier weighting from an intellectual property law and policy perspective.

Finally, it is noteworthy that there were significant numbers of generic approvals, patents and chemicals in the Total Approval, MP Approval, MP Patent, and MP Chemical Cohorts. Remarkably, the fraction of generic indicators exceeded those for brand indicators in the same class. One expects to see, and indeed does, significant numbers of generic approvals in the Total Approval Cohort, but less so in the MP Approval Cohort. Not only was there a

<sup>&</sup>lt;sup>81</sup> The ranks of these drugs were: 1 Lipitor (atorvastin); 4 Nexium (esomeprazole); 8 Zyprexa (olanzapine); 9 Diovan (valsartan); 10 Risperdal; (risperidone); 13 Effexor (venlafaxine); 15 Singulair (montelukast).

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large number of approvals in the MP Approval Cohort, but also large numbers of associated patents and chemicals in the MP Patent and MP Chemical Cohorts. Moreover, there were large numbers of indicators in the "new" drug development pathway (ANDS) and the "follow-on" development pathway (SANDS). As noted above, these data likely reflect the fact that a significant proportion of brand drugs were genericized over the eight year test period. The data also have implications for the prevalence of cluster- or portfolio-based drug development in both the brand and generic drug sectors. Combined the generic approval, patenting and chemical data in the Total Approval (Table 5; Fig. 1b), MP Approval (Table 6; Fig. 2b), MP Patent (Table 7; Fig. 3b), and MP Chemical (Table 8) Cohorts suggest generic firms are following the lead of their brand counterparts, assembling strong portfolios of approvals and patents for competitive purposes.

#### B. Limitations

The first limitation of this study is that the number of approvals and drugs analyzed in the MP Approval Cohort (347; 95) is smaller than that for in the Total Approval Cohort (2,087; 608). Similarly, the number of drugs assessed with respect to the MP Patent Cohort and MP Chemical Cohort was smaller than that for the Total Approval Cohort. This owes to the fact that we completed our analysis of approvals first,<sup>82</sup> with later efforts going primarily towards patenting, patent listing and related litigation data.<sup>83</sup> It is only with this work that we returned to complete the approval data for our Northwestern study and to extend the innovation analysis in our Berkeley study to the MP Approval Cohort. Both analyses were updated from 2008 to 2010. This update reduced the size of the cohort from 2,122 to 2,087 approvals, with no change in the number of drugs approved (608). As described above, we noted no significant change in the numbers or fractions of drugs in the various approval classes after updating the values. A final consideration is that, at least in our hands, the time and resources required to expand the patent and patent listing analyses from the 16 drugs reported in our pilot study<sup>84</sup> to the full cohort of 95 drugs<sup>85</sup> and then to update this database to 2010 is not inconsiderable. To this was added the significant new task of analyzing all chemical component data from 2001 to 2010.

A second limitation of the study is that we report patenting and chemical

<sup>&</sup>lt;sup>82</sup> Sawicka & Bouchard, *supra* note 29, at 87-88.

<sup>&</sup>lt;sup>83</sup> Bouchard 2010, *supra* note 14, at 174-175.

<sup>&</sup>lt;sup>84</sup> Bouchard 2009, *supra* note 9, at 1483.

<sup>&</sup>lt;sup>85</sup> Bouchard 2010, *supra* note 14.

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data only for drugs that have already been vetted by the market and regulators to be high value drugs. Important in this regard is that vetting of drugs in the MP Approval Cohort by regulators took place much earlier in the drug development cycle compared to the Total Approval Cohort. For example, twothirds of the drugs in the MP Cohort (62 of 95) underwent some form of expedited review (16 NOC/c; 40 PR; 6 PR-NOC/c). As a result, firms in the MP Approval Cohort would be more confident in their drug development efforts compared to those in the Total Approval Cohort. This goes some way in explaining the differences in values between the Total Approval Cohort and MP Approval Cohort, which were at times substantial. For example, there were considerably more drugs in the ER classes in the MP Approval Cohort (15% NDS ER and 5% SNDS ER for Total Approval vs. 86% and 20%, respectively, for MP Approval), the fraction of brand submissions containing a NAS shot up dramatically (42% Total Approval vs. 76% MP Approval), the number of First in Class drugs was larger (21% NDS FIC and 7% SNDS FIC for Total Approval vs. 39% and 15%, respectively, for MP Approval), while the fraction of Me Too drugs decreased (79% NDS Me Too and 93% SNDS Me Too for Total Approval vs. 61% and 85%, respectively, for MP Approval). Thus, it is possible that the differences between the Total and MP Approval Cohorts would be diminished if patenting and chemical components for the full cohort of 2,087 drugs were studied. Having said this, the MP Cohorts without question represent the most desirable drug candidates for both firms and regulators. As such these cohorts are perhaps the most important to study. With time, it is hoped to increase all cohort numbers up to the full number of 2,087 drugs and associated approvals.

Finally, it has been suggested by DiMasi and colleagues that Me Too drugs are inappropriately named and should be referred to as follow-on drugs.<sup>86</sup> Moreover, these and other authors<sup>87</sup> have claimed that Me Too drugs are not necessarily lower with regard to innovative value, as asserted by a range of food and drug scholars and physicians.<sup>88</sup> The gist of these claims is that differences in the regulatory lag between related new drug approvals delay the

<sup>&</sup>lt;sup>86</sup> DiMasi & Faden, *supra* note 11, at 23; DiMasi & Paquette, *supra* note 11 at 2. Both articles cite the following study for their claims: Bernard A. Kemp, *The Follow-on Development Process and the Market for Diuretics*, DRUG DEVELOPMENT AND MARKETING 255 (Robert B. Helms ed., 1975).

<sup>&</sup>lt;sup>87</sup> Cohen & Kaitin, *supra* note 11. *See also* references in DiMasi & Paquette, *supra* note 11.

<sup>&</sup>lt;sup>88</sup> See generally ANGELL, supra note 10; AVORN, supra note 10; GOOZNER, supra note 10; PHILIP J. HILTS, PROTECTING AMERICA'S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION (Alfred A. Knopf ed. 2003); LOVE, supra note 10.

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entry of many drugs that would otherwise be First in Class. As a result these drugs are designated Me Too drugs, along with the stigma of such designation.<sup>89</sup>

Supposing this is true, it becomes theoretically possible that a certain fraction of NDS Me Too drugs identified in this study are in effect NDS FIC drugs. According to data from DiMasi and colleagues,<sup>90</sup> a maximum of 30% of NDS Me Too drugs approved between 1990 and 2003 that had a new drug submission filed before the FIC drugs was approved. This value decreases to 17% and 15% in the 1980s and 1970s, respectively. To maximize the hypothetical difference to the present study, the highest value of 30% is used.

Assuming that 30% of NDS Me Too drugs could be NDS FIC drugs, the maximum impact would be 3.3-5.4% of all approvals, depending on the cohort. This result is arrived at owing to the low number of NDS Me Too drugs when compared to SNDS Me Too drugs. For example, NDS Me Too approvals in the MP Approval Cohort accounted for 11% of total approvals; 30% of this value amounts to a maximum increase in NDS FIC drugs of 3.3% of all drugs approved. The difference increases slightly when data from the Total Approval Cohort are analyzed. Here, NDS Me Too drugs accounted for 18% of all approvals, rendering the fraction of total results different by a maximum of 5.4%. Thus, when expressed as impact on the total number of approvals, accounting for the possibility that a significant fraction of NDS Me Too drugs are NDS FIC drugs makes very little difference.

When only brand approvals are analyzed, NDS and SNDS Me Too drugs in the Total Approval Cohort amount to 87.6% of all brand approvals. Of these, 71.2% are SNDS Me Too drugs. If 30% NDS Me Too drugs were NDS FIC drugs, still 84.6% of all drugs would be Me Too drugs and 85% of these would be SNDS Me Too drugs. Regarding the MP Approval Cohort, combined NDS and SNDS Me Too drugs currently account for 85% of all brand approvals, 70% of which are SNDS Me Too drugs. If 30% NDS Me Too drugs were NDS FIC drugs, then 77.5% of all drugs would be still be Me Too drugs, and 90% of these would be line extension Me Too drugs. Thus, the possibility that a significant fraction of NDS Me Too drugs are NDS FIC drugs has no significant impact on the conclusion that Me Too drugs, and especially line extension Me Too drugs, represent the most significant class in this study.

The greatest potential impact would be on the NDS MI drug class. Using raw numbers, 30% of 31 NDS Me Too drugs adds a further nine NDS FIC drugs, which is not insignificant compared to the current number of 20 NDS

<sup>&</sup>lt;sup>89</sup> DiMasi & Faden, *supra* note 11, at 23.

<sup>&</sup>lt;sup>90</sup> *Id.* at 25, Figure 1b.

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FIC drugs. This increase would impact the number of NDS MI drugs because the NDS FIC class is the lowest common denominator for the NDS MI calculation. As a result, NDS MI drugs would increase from 5.7% of all drug approved to 8.4% of approved drugs in the MP Approval Cohort, again not an insignificant rise in the most innovative drugs. Projecting the result of DiMasi and colleagues onto the Total Approval Cohort makes no difference at all to the NDS MI value. This is because the NDS MI value is limited by the lowest common denominator of the NDS ER class as opposed to the NDS FIC class.

To summarize, assuming that a maximum of 30% of all NDS Me Too drugs are NDS FIC drugs changes the major findings of this study by only a small amount and does not change the primary conclusions. When the total database of approvals is assessed, the results are altered by 3.3% in the MP Approval Cohort and 5.4% in the Total Approval Cohort. Looking only at brand submissions, assuming that a maximum of 30% of all NDS Me Too drugs are NDS FIC drugs changes the number of combined NDS and SNDS Me Too drugs and the fraction of these that are SNDS Me Too drugs by 3% and 13%, respectively in the Total Approval Cohort. In the MP Approval Cohort, the numbers are different by 9% and 5%, respectively. The impact on the NDS MI class is 2.7% and 0% in the MP Approval and Total Approval Cohorts, respectively. The effect on all other drug classes would be negligible. The primary finding that the single drugs class that dominates all approval, patenting and chemical component data is the SNDS Me Too class is not altered. Therefore, all major conclusions in this study remain essentially unchanged.

The extent to which the data would alter calculations presented here however is based on the assumption that DiMasi and colleagues are indeed correct (there have been no studies directly on point by other authors as yet, particularly studies that are not funded by the pharmaceutical industry) and that there is perfect coherence between the methods used by DiMasi and colleagues and in the present study. The hypothetical discussed above would be altered to the extent that there is a difference between Canadian and US regulatory data or in the methods used by both groups to calculate new and follow-on FIC and Me Too drugs.

Indeed, there are significant differences in the methods for calculating FIC and Me Too drugs in the studies that limit the conclusions arrived at above. To begin with, the method outlined in this report effects a clear empirical separation between Me Too, NAS and ER classes, both within the new (NDS) and follow-on (SNDS) approval streams. This substantially weakens the direct comparison of Me Too and First in Class drugs in the two studies. The method outlined here permits calculation of data within the same discrete drug classes

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and nomenclature used by drug regulators. These drug classes can be combined, as in the work of DiMasi<sup>91</sup> and others,<sup>92</sup> but any assessment of discrete classes is impossible unless the data are first calculated to the same degree of discrimination used by regulators.

In the original DiMasi and Paquette paper,<sup>93</sup> as well as the subsequent DiMasi and Faden study,<sup>94</sup> candidates for analysis were those that by necessity comprised New Chemical Entities (analogous to a NAS in the current nomenclature) and/or drugs that also underwent some form of priority review (analogous to ER in the current nomenclature). This narrows the range of "Me Too" candidates considerably from the method outlined in the present study. The result is that the interpretation of DiMasi and colleagues that Me Too drugs approved via the "new drug" (NDS) approval route that also have NDS ER and NDS NAS designations may be more valuable than recognized is entirely reasonable and is consistent with the findings reported here. The basis for this conclusion is that such drugs approximate the current definition of an NDS MI, which we<sup>95</sup> and others<sup>96</sup> consider the most innovative drug class of all available options. In this sense, the results of DiMasi and work by our group converge.

For scholars and policy-makers it is critical to carefully distinguish the definition of various types of Me Too, First in Class and other drug classes when comparing studies. This pertains both to drug classes and the sources of data used for analysis. Indeed, both often differ across studies and can, at times, render direct comparison of results impossible. Careful distinction between new and follow-on drug classes is particularly important in jurisdictions with some form of pharmaceutical linkage as, depending on the method used to list patents on the patent register,<sup>97</sup> patents can be listed against both new (NDS) and follow-on (SNDS) drugs. As a result, generic entry on widely used drugs coming off patent protection may be forestalled by a combination of follow-on drugs and related patents. As a result it is imperative to know precisely which classes of drugs can be used for this purpose. A final

<sup>&</sup>lt;sup>91</sup> DiMasi & Faden, *supra* note 11; DiMasi & Paquette, *supra* note 11.

<sup>&</sup>lt;sup>92</sup> Steven G. Morgan et al., *Breakthrough Drugs and Growth in Expenditure on Prescription Drugs in Canada*, 331 BRIT. MED. J. 815, 815 (2005).

<sup>&</sup>lt;sup>93</sup> DiMasi & Paquette, *supra* note 11, at 3.

<sup>&</sup>lt;sup>94</sup> DiMasi & Faden, *supra* note 11, at 24.

<sup>&</sup>lt;sup>95</sup> Bouchard 2009, *supra* note 9; Bouchard 2011, *supra* note 14.

<sup>&</sup>lt;sup>96</sup> CHANGING PATTERNS, *supra* note 40; Drugs in 2001, *supra* note 10; Editorial, *supra* note 69; Kaitin et al., *supra* note 69; Lexchin, *supra* note 10; Motola et al., *supra* note 69; New Medicines in 2007, *supra* note 69.

<sup>&</sup>lt;sup>97</sup> Bouchard 2011, *supra* note 14.

caveat is that the number of drugs designated by the FDA to satisfy criteria for priority review has escalated since this agency was obliged to terminate its practice of calculating the innovative value of approved drugs.<sup>98</sup> This may tend to artificially increase the number of drugs designated by DiMasi et al. to fulfill their study criteria. Finally, many drugs that run the approval gauntlet in the Canadian regulatory system have frequently already done so either in the United States, European Union, or both. To the degree this is true, and to the extent that second, third etc. entrants have learned and adapted to the regulatory experiences of first movers, the regulatory gap between alleged NDS Me Too and NDS FIC drugs may be shortened accordingly.

In addition to methodological issues, there are public health and economic considerations relating to Me Too drugs that may help to shape a minimal impact of regulatory delay in the context of a drug development preference for Me Too and other follow-on drugs. According to Hollis,<sup>99</sup> there are several grounds on which to conclude that a drug development preference (or indeed a regulatory preference) for Me Too drugs harms innovation and may pose risks to patients that might not otherwise materialize. For example, to the extent that Me Too drugs have similar safety, efficacy and efficiency profiles to already market products they diminish the incentive for pioneering drug development (R&D and marketing budgets being a zero sum game). From a public welfare perspective either a regulatory or drug development preference for follow-on drugs is increasingly wasteful to the extent that the resulting basket of Me Too drugs is undifferentiated. A lack of differentiation leads to a decrease in profits of brand pharmaceutical firms,<sup>100</sup> and thus will tend to reduce product diversity,<sup>101</sup> especially for new and truly innovative drugs. Some evidence for the latter claim comes in the form of decreasing trends over approximately the last decade for several classes of new drugs,<sup>102</sup> which has been accompanied by reciprocal increases in several classes of follow-on drugs, including Me Too drugs.103

<sup>&</sup>lt;sup>98</sup> Donald W. Light, *Bearing the Risks of Prescription Drugs*, in THE RISKS OF PRESCRIPTION DRUGS, 3, 33 n.23 (Donald W. Light ed., 2010).

<sup>&</sup>lt;sup>99</sup> Hollis, *supra* note 10.

<sup>&</sup>lt;sup>100</sup> Frank R. Lichtenberg & Tomas Philipson, *The dual effects of intellectual property regulations: within- and between-patent competition in the US pharmaceutical industry*, 45 J. LAW ECON. 643, 662-663 (2002).

<sup>&</sup>lt;sup>101</sup> Avanish K. Dixit & Joseph E. Stiglitz, *Monopolistic Competition and Optimum Product Diversity*, 67 AM. ECON. REV. 297, 301 (1977); Michael Spence, *Product Selection*, *Fixed Costs*, and *Monopolistic Competition*, 43 REV. ECON. STUD. 217, 234 (1976).

<sup>&</sup>lt;sup>102</sup> Sawicka & Bouchard, *supra* note 29, at 18.

<sup>&</sup>lt;sup>103</sup> Bouchard 2009, *supra* note 9, at 1507.

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In addition to creating potential mortality or morbidity harms for consumers as a result of altered benefit:risk profiles,<sup>104</sup> which ironically has also been claimed to be a justification for Me Too drugs,<sup>105</sup> an important observation with regard to patent and linkage policy is that a good deal of the harm of a preference for Me Too or other follow-on drugs is relative to the production of truly new and innovative drugs. As noted previously, too much of a focus on Me Too drug development in the context of largely undifferentiated products is that "competitive returns may be inadequate to stimulate investment into research and development."106 As discussed elsewhere,107 a regulatory preference for follow-on drugs can result in unintended consequences such as those discussed above, particularly if firms are aiming ex ante at regulatory targets provided for by law. As noted by the Supreme Court of Canada, it is understandable that pharmaceutical firms will avail themselves of regulatory incentives allowing product evergreening after the original patent has expired where it maximizes the benefit and minimizes the risk to shareholders.<sup>108</sup> The burden of policing the balance between the public and private interests in therapeutic product development thus falls squarely on the shoulders of national governments, law-makers and regulators.

#### C. Relevance to Pharmaceutical Law and Policy

The purpose of this study was to develop a unified method to collect, compare and quantify regulatory approval, patenting and chemical compound data from multiple cohorts of new and follow-on drugs that encompassed all drug classes enumerated, described and prioritized by domestic drug regulators. This reflected a desire to harmonize and bring together the lessons learned in our earlier studies under one analytical roof. A secondary purpose

<sup>&</sup>lt;sup>104</sup> ANGELL, *supra* note 10.

<sup>&</sup>lt;sup>105</sup> DiMasi, *supra* note 11, at 11 and n. 3.

<sup>&</sup>lt;sup>106</sup> Hollis, *supra* note 10, at 1189.

<sup>&</sup>lt;sup>107</sup> Bouchard 2009, *supra* note 9, at 1514.

<sup>&</sup>lt;sup>108</sup> AstraZeneca, [2006] S.C.R. 560, 2006 SCC 52 ¶ 39. Discussing the "general" relevance requirement articulated by the Federal Court of Appeal in Eli Lilly Canada Inc. v. Canada [2003] FCA 24 (Can.), Justice Binnie stated,

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

was to go beyond simplified and at times confusing descriptors of "new" and "follow-on" drugs in the literature, and to categorize the various classes of new, line extension and generic approvals according to the detailed nomenclature used by regulators themselves. Efforts in this regard were aimed at bringing analytical clarity to the type of drugs that constitute new and follow-on drugs and any regulatory preferences that may exist with respect to drug approval by regulatory agencies.

The results described in this article provide targeted data relating to a range of discrete classes of new and follow-on drugs. The term "new drug" is used narrowly to refer only to classes of drugs approved via the new drug submission route (NDS). The term "follow-on drug" is used narrowly to refer to those classes of drugs approved via the line extension (SNDS) and generic (ANDS; SANDS) approval routes. Drugs can be approved in both new and follow-on approval pathways that have Me Too, FIC, and ER designations. The two designations unique to the new category are the NDS NAS and NDS MI designations, for reasons discussed in the Methods *supra*. This framework removes any uncertainty or ambiguity regarding approval nomenclature, such as whether certain drugs should be called new or follow-on, follow-on or Me Too, and whether the Me Too and First in Class designations refer only to drugs approved via the new drug approval route or should also refer to drugs that are line extensions.<sup>109</sup>

In the nomenclature described here, there are several classes of new and follow-on drugs, and Me Too drugs can properly be considered either new or follow-on drugs depending on whether they are approved by regulators explicitly via the new (NDS) or line extension (SNDS) approval routes. The distinction gains further importance with respect to the listing of patents on the patent register under linkage laws, because such patents can be associated with either NDS or SNDS approvals. Whether drugs in a given class, including Me Too drugs, are considered new drugs or a line extensions drugs has further importance to determining the validity of products clusters and patent portfolios in the pharmaceutical sector, and the impact of such clusters on cumulative market exclusivity, and hence public health costs.

As discussed in Section VI.A. supra, the vast majority of drug approvals,

<sup>&</sup>lt;sup>109</sup> DiMasi, *supra* note 11; DiMasi & Faden, *supra* note 11, at 27; Joseph A. DiMasi & Cherie Paquette, *The Economics of Follow-on Drug Research and Development Trends in Entry Rates and the Timing of Development – The Authors' Reply*, 23 PHARMACOECONOMICS 1193, 1195 (2005); Kemp, *supra* note 86; Morgan et al., *supra* note 92.

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drug patents and chemical components were in relation to Me Too drugs and in particular line extension, or SNDS, Me Too drugs. This was true for the entire cohort of 2,087 drugs approved between 2001 and 2008 (updated to 2010) and for the smaller cohort of 95 of the most profitable drugs. The finding that the majority of indicators fall in the line extension Me Too class is inconsistent with a great deal of patent and innovation policy.<sup>110</sup> This is true also of public policy underpinning pharmaceutical linkage in both originating jurisdictions,<sup>111</sup> which has been created specifically to encourage the development of "new and innovative" pioneering therapies. Indeed, the argument in favour of the nexus between innovation and patenting in the pharmaceutical industry has been made consistently and with vigour for over a half-century.<sup>112</sup> The major grounds for this claim are that R&D activities by multinational firms are responsible for most new and innovative medicines,<sup>113</sup> and that a major justification for high drug prices is that such profits are necessary to underpin the development of new and innovative drugs.<sup>114</sup> The results presented in this paper take issue with these claims, instead supporting the notion that drug companies may be taking aim at legal targets provided by law ex ante rather than focusing on pioneering drug development.

The data presented here are consistent with results from our earlier work in the field, as well as data from previous studies in North America and the European Union. For example, the Canadian Patented Medicines Prices Review Board (PMPRB)<sup>115</sup> released data to the effect that of drugs approved between 1996 and 2000, 44.8% were line extensions and 49.6% were new

<sup>&</sup>lt;sup>110</sup> BESSEN & MEURER, *supra* note 3, at 90-91; BOLDRIN & LEVINE, supra note 3.; *See also*, *e.g.*, Adam B. Jaffe, The U.S. Patent System in Transition: Policy Innovation and the Innovation Process, 29 RES. POL'Y 531 (2000); Roberto Mazzoleni & Richard R. Nelson, The Benefits and Costs of Strong Patent Protection: A Contribution to the Current Debate, 27 RES. POL'Y 273 (1998); Robert P. Merges, *As Many as Six Impossible Patents Before Breakfast: Property Rights for Business Concepts and Patent System Reform*, 14 BERKELEY TECH. LJ. 577, 592 (1999); Keith Pavitt, *Policies for Technical Change: Where are the Increasing Returns to Economic Research?*, 93 PROC. NAT'L ACAD. SCI. 12693 (1996).

<sup>&</sup>lt;sup>111</sup> Bouchard 2011, *supra* note 14.

<sup>&</sup>lt;sup>112</sup> See generally ANGELL, supra note 10; AVORN, supra note 10; HILTS, supra note 88.

<sup>&</sup>lt;sup>113</sup> A.F. Holmer, Testimony by President and CEO of Pharmaceutical Research and Manufacturers of America on "Prescription Drug Safety and Pricing" before the Senate Committee on Health, Education, Labour and Pensions, Congressional Record, 147, no 73 (2000).

<sup>&</sup>lt;sup>114</sup> John A. Vernon, *Simulating the Impact of Price Regulation on Pharmaceutical Innovation*, 1 PHARM. DEV. & REG. 55, 55-56, 62-63, 65 (2003).

<sup>&</sup>lt;sup>115</sup> PATENTED MEDICINE PRICES REVIEW BOARD, ANNUAL REPORT 2000 (2001), *available at* http://www.pmprb-cepmb.gc.ca/English/View.asp?x=113&mp=91.

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versions of marketed drugs with moderate, little, or no improvement. Only 5.5% of all drugs approved represented a substantial therapeutic advance. In their brief note, Morgan et al.,<sup>116</sup> also using external PMPRB data, found that 6% of all drugs approved between 1990 and 2003 were breakthrough drugs, defined somewhat broadly as the ability to "effectively treat" an illness or which provides a "substantial improvement" over existing products. This number not surprisingly jumped to 12% when this already wide definition was expanded to encompass line extensions (SNDS drugs). The authors concluded that 80% of local spending could be accounted for by drugs that did not offer a substantial improvement on less expensive already marketed drugs. Similar results to those obtained using PMPRB data were reported in a study of the French prescription drug market, where 3% of drugs approved between 1981 and 2001 were deemed to be the most innovative drugs, while drugs with some important therapeutic gain and those with little to no therapeutic gain represented 8% and 89% of total approvals, respectively.<sup>117</sup>

In a study of drugs approved in the United States by the FDA between 1978 and 1989,<sup>118</sup> 14.7% of approvals had the strongest innovation rating, whereas 34.5% and 49.5% were deemed modestly or weakly innovative, respectively. A later study of FDA approvals<sup>119</sup> demonstrated that of all drugs approved between 1989 and 2000, 15%, 28%, and 57% were deemed to be the most innovative, moderately innovative, and modestly innovative, respectively. As discussed recently by Light and colleagues,<sup>120</sup> 2-3% of drugs approved over the last two decades are pioneering in nature, based on a review of evidence relating to therapeutic benefit and harm. The authors suggest the low numbers of truly innovative drugs globally match up well with the percentage (1.3%) of sales revenues spent on R&D expenditures for new drugs.<sup>121</sup> Of interest from a

<sup>&</sup>lt;sup>116</sup> Morgan et al., *supra* note 92, at 815.

<sup>&</sup>lt;sup>117</sup> Drugs in 2001, supra note 10, at 59; Editorial, supra note 69 at 68; Lexchin, supra note 10, at 243; New Medicines in 2007, supra note 69 at 79-80.

<sup>&</sup>lt;sup>118</sup> Kaitin et al., *supra* note 69, at 17–24.

<sup>&</sup>lt;sup>119</sup> CHANGING PATTERNS, *supra* note 40, at 8.

<sup>&</sup>lt;sup>120</sup> Light, supra note 98, at 5 (citing A Look Back at Pharmaceuticals in 2006: Aggressive Advertising Cannot Hide the Absence of Therapeutic Advances, 16 PRESCRIRE INT'L 80 (2007)); P.E. Barral, 20 Years of Pharmaceutical Research Results Throughout the World: 1975-1994 (Paris: Rhône-Poulenc Rorer Found. 1996).

<sup>&</sup>lt;sup>121</sup> Light, *supra* note 98, at 5-6. See James Love, Evidence Regarding Research and Development Investments in Innovative and Non-Innovative Medicines, CONSUMER PROJECT ON TECH. 15-18 (Sept. 22, 2003), http://www.cptech.org/ip/health/rnd/evidenceregardingrnd.pdf for a similar conclusion that, based on IRS data, eight to nine percent of pharmaceutical R&D budgets are directed to the

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regulatory preference perspective, of all new drugs approved by the FDA, one in seven offers a significant therapeutic advantage over existing therapies while two in seven yield adverse events serious enough to prompt the FDA to require a label change.

Our results are consistent with data from the studies reviewed above, and extend and expand this work by providing highly detailed data on various classes of new and follow-on drugs employed by drug regulators and government agencies regulating the listing of patents on the patent register under linkage laws. Importantly, the results provide an objective evidencebased nomenclature for identifying the most innovative drugs (NDS MI) and the drug classes relevant to this designation (NDS ER; NDS FIC; NDS NAS).

A further distinction between the results presented in the present work and those of others is that the data used here were obtained at arm's length to publicly disclosed results provided to scholars by government officials in the form of Annual Reports or privately disclosed results provided to scholars by pharmaceutical companies. While developing a novel scientific method for either obtaining or analyzing data is fraught with its own problems, this step nevertheless forms a necessary component of the "trial and error" heuristic typical in the hard sciences.

As reviewed in detail in the companion study,<sup>122</sup> data from earlier American, Canadian, French, and Spanish studies occurred in the context of patent laws and linkage laws having the same or very similar policy goals and objectives as those governing the present study. Therefore, it seems reasonable to conclude that global pharmaceutical firms are more focused on gaining intellectual property rights and prolonging market exclusivity for drug products with relatively low levels of innovation using available legislation and regulatory mechanisms as opposed to pioneering drug development. Given the legal duty on pharmaceutical executives to enhance shareholder value combined with the presence of legal loopholes in patent, food and drug and linage laws that yield a regulatory preference for follow-on drugs, the development of this scenario is not only entirely reasonable, but rather straightforward and predictable.

The data provided in this study may also help to identify areas in which government could provide rational evidence-based innovation incentives to pharmaceutical firms for their R&D efforts. For example, in order to produce more NDS MI drugs, the results here demonstrate it is necessary to produce more drugs undergoing expedited review (NDS ER), drugs containing a NAS

development of new drugs, eighty percent of which is spent on developing drugs that have "no significant improvement over marketed products."

<sup>&</sup>lt;sup>122</sup> QIP II Companion Paper, *supra* note 8, at 37, 67.

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(NDS NAS), and particularly drugs with a First in Class designation (NDS FIC). The data clearly show that the 'lowest common denominator' for the NDS MI class is most frequently the NDS FIC class, though in the Total Approval Cohort it is the NDS ER designation. Thus, not only could more R&D be aimed at NDS FIC and NDS ER drug development, but perhaps a greater share of intellectual property or regulatory rights incentives as well. This would be particularly true of data or market exclusivity periods, which could be tailored to incent specific drug class targets such as NDS FIC, NDS ER, and NDS NAS drugs without changing the evidentiary standards for approval in these classes.

Finally, the broad array of line extension approvals, patents and chemical components reported here is consistent with the conclusion that the main vehicle of achieving prolonged market exclusivity on a basket of related drug products is cluster-based drug development.<sup>123</sup> In this scheme, the spatiotemporal growth of portfolios of patents and related products is aided by the iterative effect of linkage laws working in tandem with low standards for drug approval and drug patenting. The results from our studies in combination with those undertaken in other jurisdictions parallel the growing body of empirical data relating to the effectiveness of patents to incent pioneering innovation,<sup>124</sup> including in the pharmaceutical sector.<sup>125</sup> This issue is discussed more fully in the companion paper.<sup>126</sup>

#### VI. SUMMARY & CONCLUSIONS

The purpose of this study was to develop a harmonized method to collect, compare and quantify data from a single cohort of drugs at the same level of detail described in regulatory documents and in the pharmaceutical innovation literature. A related purpose was to address uncertainty in the literature regarding approval nomenclature, such as whether certain drugs should be called new or follow-on, follow-on or Me Too, and whether the Me Too and First in Class designations refer only to drugs approved via the new drug

<sup>&</sup>lt;sup>123</sup> Kingston, *supra* note 75, at 235-27; Parchomovsky & Wagner, *supra* note 4, at 2, 5-8, 27-30, 32-33, 39; Bouchard 2011, *supra* note 14, at 392-96, 400-01, 443-45; RON A. BOUCHARD, PATENTLY INNOVATIVE: HOW PHARMACEUTICAL FIRMS USE EMERGING PATENT LAW TO EXTEND MONOPOLIES ON BLOCKBUSTER DRUGS 8, 190, 195, 207, 221, 244-47, 250-52 (2011) (2011).

<sup>&</sup>lt;sup>124</sup> BESSEN & MEURER, *supra* note 3. For recent articles on patent value, including data on pharmaceutical patents, *see*, *e.g.*, Lemley, *supra* note 4; Parchomovsky & Wagner, *supra* note 4.

<sup>&</sup>lt;sup>125</sup> BOLDRIN & LEVINE, *supra* note 3.

<sup>&</sup>lt;sup>126</sup> QIP II Companion Paper, *supra* note 8, at 11-14, 37-39, 51-52, 60-65, 67.

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approval route or should also refer to drugs that are line extensions. The term "new drug" is used narrowly to refer only to classes of drugs approved via the new drug submission route (NDS). The term "follow-on drug" is used narrowly to refer to those classes of drugs approved via the supplementary or line extension (SNDS) and generic (ANDS; SANDS) routes. Moreover, the ER, Me Too, and FIC designations apply to drugs approved in both the NDS and SNDS categories. This removes any uncertainty or ambiguity regarding approval nomenclature.

Approvals, patents and chemical components were analyzed across numerous classes within the broader categories of new and follow-on drugs. This included approvals granted to brand-name drug companies in the new drug approval route (NDS) that were directed to First in Class drugs (NDS FIC), Me Too drugs (NDS Me Too), drugs containing an New Active Substance (NDS NAS), drugs undergoing one of the two pathways for expedited review (NDS ER) and drugs deemed to be the most innovative (NDS MI). Drugs moving through the new drug approval route that did not have an extra designation (NDS) were also studied. Line extension approvals granted to brand pharmaceutical firms via the follow-on pathway were studied alone (SNDS) or in conjunction with FIC (SNDS FIC), Me Too (SNDS Me Too), and ER (SNDS ER) designations. Finally generic drugs undergoing conventional (ANDS) and follow-on (SANDS) abbreviated review were studied alone or in combination.

Altogether, there were 13 distinct classes of new and follow-on drugs analyzed. Each of the thirteen classes was analyzed in relation to drug approvals, drug patenting, and chemical components. Approval and patenting data were studied in order to investigate the characteristics of innovation and drug development in the pharmaceutical sector. Chemical components were studied in order to gain information regarding potential cluster-based product development strategies and to determine if and how firms were developing chemical derivatives for line extension products.

Drug approval data were analyzed in relation to all drugs approved domestically between 2001 and 2008. This yielded a cohort of 2,087 approvals associated with 608 drugs referred to as the Total Approval Cohort. We also analyzed 347 approvals relating to a smaller cohort of 95 of the most profitable drugs sold between 2001 and 2008. This cohort is referred to the MP Approval Cohort. In addition to approvals, we also analyzed 5,011 patents and 130 chemical components associated with the MP Approval Cohort. These groups are referred to as the MP Patent and MP Chemical Cohorts, respectively. This yielded a basket of 52 drug classes across the four cohorts for harmonized analysis. In addition to parsing the raw numbers in this manner, data were

normalized in three ways: as percentage of brand new and follow-on submissions individually or as a fraction of the combined total as well as a percentage of combined brand submission types.

Several important trends in the data emerged across drug classes and indicators. The first and most important of these is that the greatest fraction of all approvals, patents and chemicals studied were in the Me Too class, particularly in the follow-on or SNDS Me Too class. As a result, a primary finding in this study is that the vast majority of drug approvals, drug patents, and related chemical components are associated not with new drugs, but rather with follow-on drugs. Calculated as a percentage of total brand indicators, the Me Too class accounted for 89% of approvals in the Total Approval Cohort, 81% of approvals in the MP Approval Cohort, 94% of patenting in the MP Patent Cohort, and 82% of all chemicals in the MP Chemical Cohort.

Of the total group of Me Too drugs in the Total Approval Cohort, the vast majority were line extension, or SNDS, Me Too drugs. There were 245 and 976 NDS and SNDS Me Too drugs, respectively. Thus, there were 400% more line extension Me Too drugs compared to Me Too drugs in the new drug approval pathway. The difference was even greater in the Most Profitable Approval Cohort. Here, there were 31 and 194 NDS and SNDS Me Too drugs, respectively, representing a 530% increase in Me Too drugs approved via the line extension route compared to the new drug approval route. A similar pattern was observed for patenting and chemical components. There were 742 and 2,514 patents in the NDS and SNDS Me Too classes, respectively. This represents a 340% increase in patenting associated with line extension compared to new Me Too drugs. Of all patents associated with Me Too drugs, 77% were in relation to SNDS Me Too drugs. Of 112 chemicals associated with patents granted to brand firms, a remarkable 62, or 55%, were directed to SNDS Me Too drugs.

The data discussed thus far demonstrate that the majority of approval, patenting and chemical development activity associated with brand pharmaceutical products is directed to the development of Me Too drugs, in particular line extension drugs (SNDS Me Too). This raises the question of whether the combination of regulatory and economic incentives for line extension drugs is driving drug development. There is no question that the evidentiary threshold for various new and follow-on drugs allows for a wide array of new uses and chemical derivatives, including solvates, fillers, crystalline forms, salt forms, racemic forms, dosage forms, etc. Regarding market incentives, as indicated by sales figures from the year 2006, there is clear and convincing evidence incenting the development of Me Too and line extension drugs over other drug classes. For example, of the top 25 most

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profitable drugs in 2006, 12, or 48%, of the data set described here were line extension Me Too drugs. In 2006 alone, these products had combined sales of US \$45.7 billion dollars. Similarly, line extension FIC drugs represented 28% of the top 25 selling drugs, and 7 of the top 15 selling drugs. Profit on this group of drugs was US \$39.7 billion dollars in 2006. Combined, line extension Me Too and FIC drugs accounted for 19 of the top 25 most profitable drugs, for a total of US \$85,470,000 in sales in a single year.

Despite the overwhelming dominance of Me Too and line extension drugs, there is also good news regarding pharmaceutical innovation. The second trend in the data is towards a growing percent total for line extension (SNDS) and new (NDS) drugs undergoing some form of expedited review (NDS ER; SNDS ER) and drugs approved via the new drug submission route that contained a new active substance (NDS NAS). This trend was observed across indicators. Within the three MP Cohorts specifically there was a slow but steady decline in the fraction of total Me Too indicator that was in the line extension or SNDS class. This declined from 86% of all Me Too approvals in the MP Approval Cohort to 71% of Me Too patents in the MP Patent Cohort to 67% of Me Too chemicals in the MP Chemical Cohort. Combined, these data suggest that as one moves, including within the MP data set itself, from approval to patenting to chemical data, there is an increasing incidence of brand firms focusing on classes other than SNDS Me Too drugs. The two most noticeable examples of this reversal are for NDS ER and NDS NAS drugs in the MP Chemical and MP Patenting indicators. Thus, while brand firms appear to be putting most of their effort into developing Me Too drugs, drugs moving through one of the two pathways for expedited review and drugs with a New Active Substance are also receiving significant attention.

The third general trend is that the percent of drugs that satisfied the criteria for most innovative (NDS MI) was limited across all four Total Approval, MP Approval, MP Patent and MP Chemical Cohorts by the comparatively lower number of NDS FIC values and to a lesser extent the NDS ER value. As a reminder, NDS MI drugs are those going through the new drugs approval route and which contain a new active substance (NDS NAS), are First in Class (NDS FIC), and undergo some form of expedited review (NDS ER). It is not surprising that the NDS FIC class limits the innovation value for most of the cohorts studied, as NDS FIC drugs are those that consist of either a brand new family of active ingredient(s) or old active ingredient(s) used for the treatment of a new indication. Therefore, a drug is deemed to be a new First in Class drug only where there is no other drug on the market that belongs to the same compound family and is used for the same indication e.g., where there is no comparator.

The scenario for the NDS FIC class differs substantially from other pathways for gaining regulatory approval involving chemical changes. For example, SNDS status can be achieved by a wide array of chemical modifications, including amendments to dosage, strength, formulation, manufacture, labeling, route of administration, or indication. Similarly, NDS NAS status may be achieved a chemical or biological substance not previously approved for sale as a drug or an isomer, derivative, or salt of a chemical substance previously approved for sale as a drug but differing in properties with regard to safety and efficacy. Thus, compared to NDS FIC drugs, which cannot have been sold domestically in that chemical form, there is a relatively wide evidentiary berth for the development of new chemical forms for both the new and follow-on drug approval routes, including for the SNDS FIC class. For this reason, both the evidentiary threshold and difficulty of drug development is greater for NDS FIC drugs compared to SNDS FIC drugs.

For the reasons discussed above, it is not surprising that the more profitable approach is for developers to focus their efforts on drugs in the line extension (SNDS FIC) category as opposed to those in the new drug category (NDS FIC). Indeed, there were 70% and 96% more approvals and patents in the SNDS FIC class compared to the NDS FIC class in the most profitable cohort. This result corresponds with the focus of brand firms on SNDS Me Too drugs more generally, as both are classes of line extensions. As noted *supra*, SNDS FIC drugs represented over one quarter of the top 25 selling drugs, and nearly half of the top 15 selling drugs; profit on this group of drugs was US \$39.7 billion dollars in 2006. Combined with data relating to SNDS Me Too drugs, the data show that financial incentives for line extension drugs parallel regulatory preferences for the same drug classes, as regulators could raise the evidentiary bar for follow-on drugs should they so desire.

The fourth general trend was the observation that, using the NDS MI classification system to assess the degree of innovation, there was a strong trend towards increasing levels of innovation as one moved from drug approvals to drug patents and finally to chemical components. The NDS MI values increased steadily from the Total Approval Cohort (1.1%) to MP Approval Cohort (5.3%) to the MP Patenting Cohort (11%) and the Chemical Cohort (15%). These data suggest that the utility of indicators to firms is chemicals > patents > approvals. This is consistent with the observation in our Northwestern study that there are on average 61 patent classifications per drug product, which can be used for both drug development and patent listing purposes. Having said this, only approvals and patents (and the listing of patents on the patent register) provide the legal means to obtain market authorization and maintain market exclusivity.

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It is noteworthy that the NDS FIC class represented the lowest common denominator across cohorts (except the Total Approval Cohort, where it was the second lowest value) and thus dropped the NDS MI value accordingly in each of the four cohorts. The data suggest that a focus on developing NDS FIC drugs would be an efficient way for brand firms to increase the level of innovation in their pipelines. A second conclusion is that regulators could contemplate allocating a greater share of intellectual property and regulatory rights incentives for drug classes underpinning NDS MI drug development (NDS FIC; NDS NAS; NDS ER), particularly the NDS FIC, and to a lesser degree the NDS ER, drug class. Data and market exclusivity periods could be customized to provide proportional incentives for new and follow-on drug development, especially in the classes comprising NDS MI drugs or where unmet medical need is greatest e.g., for pathways to expedited review in the new drug category (Priority Review and NOC/c).

Chemical forms were studied in order to gain an understanding of whether and how brand firms might be using a portfolio-based strategy in their drug development efforts. The reason for making this assumption was the wide berths for chemical derivatives in both new and follow-on approval pathways. The significant functional utility of chemicals with regard to line extension development in particular is supported by the data obtained. For example, of the 112 chemicals claimed in patents granted to brand firms, 64, or 57%, were associated with line extension drugs while 48, or 43%, were for new drugs. As discussed in Section V supra, the two widest berths for drug approval with regard to minimal chemical modification are the NDS NAS and SNDS classes. Therefore, it is not surprising to observe that the SNDS class contained the greatest number of chemicals, and in this category the vast majority of chemicals (n=62) were directed to SNDS Me Too drugs. This represented 97% of all SNDS chemicals and 55% of all chemicals claimed in patents granted to brand firms. In the NDS category, NDS NAS chemicals (n=39) were second only to NDS ER chemicals (n=43). These results correspond to rank order data for drug approvals in the MP Approval Cohort, where the SNDS Me Too class was the largest line extension class and the NDS NAS class was the second largest new drug approval class.

Relevant to the issue of product clusters, the ratio of approvals to chemicals was 0.91:1 and 1:1 for NDS and NDS NAS classes and 3.56:1 and 3.12:1 for SNDS and SNDS Me Too classes. In other words, there was an approximately 300% greater number of approvals per chemical for line extension drugs compared to new drugs. Thus, the utility of chemicals in the NDS NAS and SNDS, and particularly the SNDS Me Too, classes is substantial. This result provides some evidence for a product cluster-based drug development strategy

where the spatiotemporal characteristics of drug product-drug patent clusters grow over time as the market and regulators continue to vet related line extensions. While in general the patent data support this interpretation (about 70% of all patents are on SNDS drugs, while 30% are associated with new drugs), the patent to approval ratio is larger for NDS drugs (23:1) than for SNDS drugs (11:1). Clearly, more work is needed on this issue in order to quantify the relationship of patented chemical components to product clusters as well as how they evolve over time.

Fifth, there were a significant numbers of approvals, patents and chemicals granted to generic drug companies in the Total Approval, MP Approval, MP Patent, and MP Chemical Cohorts. Remarkably, the fraction of generic indicators often exceeded those for brand indicators in the same class. One might expect to see, and indeed does, significant numbers of generic approvals in the Total Approval Cohort but less in the MP Approval Cohort. However, we observed a large number of generic approvals in the MP Approval Cohort, but also large numbers of associated patents and chemicals in the MP Patent and Chemical Cohorts. Moreover, there were not only large numbers of generic indicators in the "new" generic development pathway (ANDS), but also in the "follow-on" pathway (SANDS).

The results pertaining to generic products suggest that a significant proportion of brand drugs came off patent protection over the course of this study. Moreover, generic firms appear to be accruing greater number of approvals, patents and chemical components than may have been previously recognized. Data such as these suggest that generic firms are following the lead of their sister brand firms in regards to drug development by creating substantial clusters of products and patents over time for purposes of intellectual property protection and competition.

Finally, the data and methods reported here provide the quantitative basis for developing the qualitative innovation index described in the companion paper.<sup>127</sup> The implications of the qualitative data parsed through the innovation index for global pharmaceutical law and policy, product clusters and patent portfolios, and competition issues are discussed further there.

<sup>&</sup>lt;sup>127</sup> QIP II Companion Paper, *supra* note 8, at 2-3, 16-22, 34, 46, 55-57, 66-68.