EVIDENCE OF PATENT THICKETS IN COMPLEX BIOPHARMACEUTICAL TECHNOLOGIES

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ABSTRACT

We test for the existence and the influence of patent thickets in the biopharmaceutical industry by analyzing the statistical distribution of patent licenses in the 200 top-selling drugs in the U.S. We show that: (1) a patent thicket effect is discernible when the potential seller must acquire a license from two or more patent owners in order to create a downstream commercially viable product that flows from complex (as opposed to discrete) biopharmaceutical technologies; (2) a patent thicket effect in the domain of complex biopharmaceutical technologies becomes quite pronounced when the potential seller must acquire a license from three or more patent owners; and (3) where a potential seller must acquire a license from four or more patent owners, a patent thicket effect develops that makes successful negotiation for all of the necessary licenses with the relevant patentees virtually impossible. Our findings contribute (a) to the literature on patent thickets in the biopharmaceutical industry; (b) to the perennial

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policy debate on whether patents stifle or stimulate innovation; and (3) to discussions regarding the appropriate contours of a regulatory regime that would positively nudge production of more commercially viable and socially desirable drugs that rely upon complex biopharmaceutical technologies.

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I. INTRODUCTION

A patent thicket exists when two or more parties have overlapping patent rights and a potential manufacturer must negotiate licenses with each patent owner in order to bring a product to market without infringing on the rights of the patentees.[1] Professor Carl Shapiro and others contend that such thickets are present in semiconductor, biotechnology, computer software, and the internet-

[1] Michael Noel & Mark Schankerman, *Strategic Patenting and Software Innovation*, at 2–3 (Ctr. for Econ. Pol'y Research, Discussion Paper Ser. No. 5701, 2006).

based industries.[2] Measuring the existence and the strength of patent thickets would help resolve questions regarding the circumstances in which patent protection in the biopharmaceutical industry may actually stifle innovation.[3]

We test for the existence and the influence of a patent thicket in the biopharmaceutical industry by analyzing the extent to which patent licenses were present in the 200 top-selling drugs in the United States. Our analysis of the licensing activity of these 200 drugs enables us to draw the following conclusions. First, one initially observes a thicket effect when a downstream commercial seller must acquire a license from two or more patent owners. Second, the thicket effect becomes quite pronounced when there are three or more patent owners. Third, where four or more patent owners exist, the thicket effect is so strong that a potential seller will find it virtually impossible to negotiate successfully all of the licenses necessary to create a downstream commercially viable product.

II. PATENTING AND LICENSING CHARACTERISTICS OF THE BIOPHARMACEUTICAL INDUSTRY

A. Overview of Patents and Licensing of Pharmaceuticals

Innovation should be rewarded. Patents in the biopharmaceutical industry have enabled most companies—in Europe, the United States, and South Africa—to recover their research and development (R&D) expenditures in order "to remain profitable and to have an incentive to continue investing in innovation."[4] (Regulatory changes in domestic and international markets that weaken

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2 *Id*.; *see also* Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting*, *in* 1 INNOVATION POLICY & THE ECONOMY 119 (Adam B. Jaffe et al. eds., 2001); Alberto Galasso & Mark Schankerman, *Patent Thickets, Courts, and the Market for Innovation*, 41 RAND J. ECON. 472, 475 (2010); Amit Makker, *The Nanotechnology Patent Thicket and the Path to Commercialization*, 84 S. CAL. L. REV. 1163, 1178–79 (2011).

3 Moreover, several researchers claim to have discovered fairly objective means to assess the existence of deleterious patent thickets. *See, e.g.*, *Method for the Identification of Patent Thickets*, U. OF MICH., http://inventions.umich.edu/technologies/2715/method-for-identification-of-patent-thickets (last visited Sept. 20, 2012) (providing a "methodology for a systematic approach to identifying close groupings of patents within the Intellectual Property Landscape").

4 EUR. ASS'N OF EURO-PHARMACEUTICAL COS., FOR A STRONG AND INNOVATIVE EUROPEAN PHARMACEUTICAL INDUSTRY 7 (2006), *available at* www.eaepc.org/admin/files/eaepc_paper_on_r&d_debate.doc; *see also* Stu Woolman & Courtenay Sprague, *Aspen Pharmacare: Providing Affordable Generic Pharmaceuticals to Treat HIV/AIDS and Tuberculosis*, *in* THE BUSINESS OF SUSTAINABLE DEVELOPMENT IN AFRICA 285 (Ralph Hamann et al. eds., 2008); Courtenay Sprague & Stu Woolman, *Moral*

patent protection may, indeed, be driving down R&D investment and impeding technology advances.)[5]

In strong intellectual property regimes, the owner of a patent may exploit its intellectual property by entering into a contract in which the patent owner—the licensor—contracts with another party—the licensee—in a manner that enables the licensee to exploit the licensor's intellectual property.[6] Philip Mendes writes as follows on licenses in the pharmaceutical sector:

> [M]ost intellectual property licenses are granted on an exclusive basis. . . . [T]he extent of speculative investment in the development, clinical and regulatory phases of taking a product to market relies upon exclusivity to warrant that speculative investment. An exclusive license is one therefore where the licensee exploits the intellectual property to the exclusion of all other people, including the licensor. . . . The licensor, by granting an exclusive license, gives up the right to exploit the intellectual property itself.[7]

Luck: Exploiting South Africa's Policy Environment to Produce a Sustainable National Antiretroviral Treatment Programme, 22 S. AFR. J. ON HUM. RTS. 337, 378–79 (2006)*;* KLAUS SCHWAB & MICHAEL E. PORTER, WORLD ECON. FORUM, THE GLOBAL COMPETITIVENESS REPORT 2008-2009 49 (2008), *available at* https://members.weforum.org/pdf/GCR08/GCR08.pdf; *see generally* Nancy T. Gallini, *The Economics of Patents: Lessons from Recent U.S. Patent Reform*, 16 J. ECON. PERSP., no. 2, 2002 at 131, 131–32 (noting that in the US, "[e]very major industrial sector has been represented in [a] surge of [patent application] activity . . . with a doubling of biotechnology patent grants . . . [as a result] of changes . . . widely perceived to have strengthened patent protection, in that patents have become easier to enforce and may be granted for longer periods of time.").

5 *See* Brian Tempest, *The Structural Changes in the Global Pharmaceutical Marketplace and Their Possible Implications for Intellectual Property*, at 1–2 (UNTAD-ICTSD Project on IPRs & Sustainable Dev., Int'l Ctr. for Trade & Sustainable Dev. Policy Brief No. 10, 2011), *available at* http://unctad.org/en/docs/iprs_in2011d1_en.pdf.

6 BRIAN G. BRUNSVOLD ET AL., DRAFTING PATENT LICENSE AGREEMENTS 6 (6th ed. 2008); NOEL BYRNE, LICENSING TECHNOLOGY: DRAFTING AND NEGOTIATING LICENSING AGREEMENTS 22 (1994); Philip Mendes, *Licensing and Technology Transfer in the Pharmaceutical Industry* 3 (2005), *extracted from* INT'L TRADE CTR., EXPORTING PHARMACEUTICALS: A GUIDE FOR SMALL AND MEDIUM-SIZED EXPORTERS (2005), *available at* http://www.wipo.int/export/sites/www/sme/en/documents/pdf/pharma_licensing.pdf.

7 Mendes, *supra* note 6, at 13–14; *see* Marissa Paslick, *"Exclusive" No Longer Means Exclusive in the Context of Patent Licenses—A Look at Why There is Value in This Ambiguity*, 19 U. BALT. INTELL. PROP. L.J. 167, 169–70 (2011) (describing the sometimes indeterminate nature of a patent's exclusivity); *see also* George Dandalides, *The Patentability of Isolated DNA Sequences Deoxyribonucleic Acid (DNA)*, 14 TUL. J. TECH. & INTELL. PROP. 283, 304–05 (2011) (addressing the complex and contested nature of such patents, the kinds of "patent races" that further confuse the legal regime that governs innovation in this relatively new domain, and the degree to which contestation between parties seeking patents or protecting patents can undermine innovation); Michael E. McCabe & Lindsay J. Kile, *Recent Develop-*

However, Mendes notes that, on occasion, "biotechnology may lend itself to the grant of numerous non-exclusive licenses by a licensor."[8] He offers as examples vaccine delivery systems, viral vectors, and cell lines as common forms of non-exclusive licenses tendered by biotechnology and pharmaceutical firms.[9]

B. Pharmaceuticals as Discrete and Complex Forms of Technology

Technology has been described as either discrete or complex in nature.[10] One example of a piece of discrete technology is an active pharmaceutical ingredient (API).[11] A patent for a drug will normally cover the molecular formula for the API.[12] By contrast, a piece of complex technology embraces a number of discrete components.[13] A personal computer (PC), for example, consists of integrated circuit chips, a video screen, memory, keyboard, software, and a mouse. One or more patents may cover each subcomponent.

One might think that discrete forms of technology would be easier to patent, license, and market than complex forms of technology. But that is not

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ments in Patent Law and Their Impact on the Pharmaceutical and Biotechnology Industries, 19 U. BALT. INTELL. PROP. L.J. 75, 102 (2011) (describing an instance in which the licensor was sued for infringement).

8 Mendes, *supra* note 6, at 14.

9 *Id.*

10 Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 880–82 (1990).

11 WORLD HEALTH ORG. WORKING DOCUMENT QAS/11.426/REV.1, DEFINITION OF ACTIVE PHARMACEUTICAL 3–4 (2011). Earlier World Health Organization (WHO) guidelines followed an erroneous definition of active pharmaceutical ingredient: "Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings." *Id.* at 3. "This definition implies, for example, that commercially available premixes of APIs (such as the popular amoxicillin + clavulanic acid premix) can be regarded as an API, which is not correct. This definition . . . lead[s] to misinterpretation." *Id.* Thus, WHO proposed changing the erroneous definition "by deleting 'or mixture of substances', in accordance with the definition already appearing in WHO Technical Report Series, No. 961, Annex 10 ." *Id.* The proposed definition defines active pharmaceutical ingredient (API) as "[a] substance used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings." *Id.* Should this definition be approved, it will apply to all future and current WHO documentation. *See id.*

12 *See id.* at 3–4.

13 Merges & Nelson, *supra* note 10, at 881–82.

necessarily so. A PC contains so many components that it may require the manufacturer and the seller to obtain licenses under numerous patents. Yet, this complexity has not been an impediment to enhancements in PC technology or to downstream sale of the final product to the consumer.[14] For example, the semiconductor industry's custom of cross-licensing has enabled electronics technology to advance rapidly and overcome potential thicket effects.[15]

The situation is quite different in the biopharmaceutical industry. Such technology is quite often discrete: virtually all that the company requires to bring a safe and efficacious drug to market is a single patented molecule.[16] The discreteness of the technology eliminates the need for cross-licensing.[17] At the same time, industry participants may use their patents to stake out proprietary, exclusionary, defensible, and inefficient positions.[18] Where complementary patents found in complex biopharmaceutical technologies are necessary for effective commercialization, manufacturers must negotiate individual licenses for any patented innovation they do not own.[19] Licensing may happen at the time

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14 *Id.* at 882.

15 *See generally* Peter C. Grindley & David J. Teece, *Managing Intellectual Capital: Licensing and Cross-Licensing in Semiconductors and Electronics*, 39 CAL. MGMT. REV. 8 (1997) (describing the prevalence of cross-licensing in the semiconductor and electronics industry).

16 *See generally* BARRY WERTH, THE BILLION DOLLAR MOLECULE: ONE COMPANY'S QUEST FOR THE PERFECT DRUG (1995) (showing how the biotech company Vertex Pharmaceuticals pioneered rational drug design that emphasized single molecule design—as opposed to combinatorial methods—so as to more easily facilitate the downstream commercial success of a drug).

17 *See id.* If you only need one patent to create a commercially viable drug, then many of the potential barriers to bringing the drug to market—i.e., preventing another firm from copying your unique design—fall away. *See* Bronwyn H. Hall, *Patents and Patent Policy*, 23 OXFORD REV. ECON. POL'Y 568, 572–73 (2007) ("Offering individuals the short-term right to exclude others from practising an invention provides the inventors with the opportunity to earn rents or supranormal profits when they innovate that are higher than those they would earn if there were immediate free entry into imitation of their invention.").

18 Ian Hastings, *Dynamic Innovative Inefficiency in Pharmaceutical Patent Settlements*, 13 N.C. J. L. & TECH. 31, 59–60 (2011); Richard C. Levin et al., *Appropriating the Returns from Industrial Research and Development*, 3 BROOKINGS PAPERS ON ECON. ACTIVITY 783, 788 (1987); Wesley M. Cohen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (Or Not)* 2 (Nat'l Bureau of Econ. Research, Working Paper No. 7552, 2000).

19 Hall, *supra* note 17, at 573 (2007) ("When development of an innovative product requires multiple patent inputs, Heller and Eisenberg . . . have argued forcefully that the licensing solution may fail because of transactions costs if a large number of patent-holders are involved.").

the drug is to be brought to market or ex ante as a condition of a joint venture.[20] In either case, patent licensing is susceptible to thicket effects.[21]

Readers might be caught short by the last set of observations. Some colleagues have suggested that if multiple licenses are not typically needed by a firm to market a new drug, then the problem of patent thickets in the biopharmaceutical industry falls away.[22] These interlocutors then speculate that since virtually no approved commercial drugs require four of more licenses, we should rather conclude that most pharmaceuticals on the market reflect the discreteness of the technology of drug innovation.[23] However, a careful analysis of the Appendix and the 200 drugs listed therein suggests a more complex, and less reductive, landscape. Given the proprietary nature of active pharmaceutical ingredients, it is virtually impossible to assess the number of potentially efficacious and commercially viable drugs that might *never* make it to market because of the formation of a patent thicket. The data set of the patents and licenses of the 200 top-selling drugs in the U.S. offers the clearest window on to the degree to which commercially viable pharmaceutical innovations flow from both discrete biopharmaceutical technologies and complex biopharmaceutical technologies.

C. Patent Thickets Theory

1. Definition of a Patent Thicket

A patent thicket is "a dense web of overlapping intellectual property rights that a company must hack its way through in order to . . . commercialize new technology."[24] A thicket can form when multiple parties own patents on components of a single drug.[25]

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20 Jerry R. Green & Suzanne Scotchmer, *On the Division of Profit in Sequential Innovation*, 26 RAND J. ECON. 20, 23 (1995).

21 James Bessan, *Patent Thickets: Strategic Patenting of Complex Technologies* 1–2 (Research on Innovation, Working Paper No. 0401, 2004) (contending that where patent standards are low, firms build thickets of patents and create suboptimal conditions for research and development, but "[o]n the other hand, when lead time advantages are significant and patent standards are high, firms pursue strategies of 'mutual non-aggression'"). R&D, on this account, benefits from strong patent regimes. *See id.*

22 *See generally* WERTH, *supra* note 16.

23 This claim was forcefully made by one anonymous reviewer of this article, but without a compelling body of evidence to support the thesis. Our evidence and analysis cuts in the opposite direction.

24 Shapiro, *supra* note 2, at 120.

25 *See* Bessan, *supra* note 21, at 1.

2. Weak and Strong Patent Thickets

Patent thickets may be strong or weak. Weak thickets exist when licenses are relatively easy to obtain.[26] Strong thickets exist when licenses are extremely difficult to secure.[27]

Ideally, multiple parties would always negotiate in their own best interest and expect a royalty neither greater nor smaller than their proportional contribution to the commercialized product. Some authors have, in fact, created algorithms that provide guidance as to the appropriate attribution of equities with respect to sequential inventions that require cross-licensing to create a marketable good.[28] Yet negotiations often break down. A popular theory—the "anticommons thesis"—contends that strong thickets are especially prevalent in biomedical research.[29] In coining this neologism, Professors Michael A. Heller and Rebecca S. Eisenberg suggest that high transaction costs, heterogeneous interests of alliance partners, cognitive biases, or attributive biases may lead to conditions under which the bargaining between parties eventually reaches an impasse.[30] The result, from which no one benefits, is that commercial activities cease.[31] The unlicensed technology remains in the laboratory and never makes it to market.[32]

According to Heller and Eisenberg, an anticommons exists "when multiple owners each have a right to exclude others from a scarce resource and no one has an effective privilege of use."[33] (A patent itself has been described as

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26 *See* Fabienne Orsi & Benjamin Coriat, *Are "Strong Patents" Beneficial to Innovative Activities? Lessons from the Genetic Testing for Breast Cancer Controversies*, 14 INDUST. & CORP. CHANGE 1205, 1208 (2005).

27 IAN HARGREAVES, DIGITAL OPPORTUNITY: A REVIEW OF INTELLECTUAL PROPERTY AND GROWTH 56–57 (2011). This study sponsored by the United Kingdom supports the contention that strong patent thickets "obstruct entry to some markets and so impede innovation." *Id.* at 5.

28 Green & Scotchmer, *supra* note 20, at 22.

29 Michael A. Heller, *The Tragedy of the Anticommons: Property in the Transition from Marx to Markets*, 111 HARV. L. REV. 621, 688 (1998).

30 Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCI. 698, 700 (1998). For more recent analysis of how the behavior of the scientific community itself shapes patents and licensing behavior, see generally Fiona E. Murray et al., *How Does the Republic of Science Shape the Patent System? Broadening the Institutional Analysis of Innovation Beyond Patents*, 1 U.C. IRVINE L. REV. 357 (2011).

31 Heller & Eisenberg, *supra* note 30, at 698.

32 *Id.* at 699.

33 *Id* at 698.

the right of an innovator to preclude the competition from exploiting a particular invention.)[34] Multiple owners each possess a patent capable of blocking use of a good necessary for the production of a viable, marketable technology.[35] An anticommons or patent thicket reflects a fragmented upstream intellectual property rights environment that impedes the collaboration between potential partners and the development of a new technology.[36] Valuable business opportunities are foregone because one or more of the intellectual property owners have made it too difficult to negotiate all the necessary licenses to create the final, downstream, marketable product.[37]

Patent thickets fly in the face of the widely accepted economic assumption that rational actors will ultimately arrive at a mutually acceptable agreement to exploit an opportunity. Professor Suzanne Scotchmer argues that prenegotiated agreements between firms can resolve ownership IP rights of downstream products.[38] But "can" does not mean "must."

The extant anticommons literature tends to suggest that high transaction costs,[39] the heterogeneous interests of rights holders,[40] the cognitive biases, and

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34 Hall, *supra* note 17, at 568.

35 Heller & Eisenberg, *supra* note 30, at 698.

36 *Id.* at 699.

37 *Id.*

38 Green & Scotchmer, *supra* note 20, at 31.

39 The transaction costs of licensing in biomedical research, Heller and Eisenberg opine, stem from four discrete sources:

> First, many upstream patent owners are public institutions with limited resources for absorbing transaction costs and limited competence in fast-paced, market-oriented bargaining. Second, the rights involved cover a diverse set of techniques, reagents, DNA sequences, and instruments. Difficulties in comparing the values of these patents will likely impede development of a standard distribution scheme. Third, the heterogeneity of interests and resources among public and private patent owners may complicate the emergence of standard license terms, requiring costly case-by-case negotiations. Fourth, licensing transaction costs are likely to arise early in the course of R&D when the outcome of a project is uncertain, the potential gains are speculative, and it is not yet clear that the value of downstream products justifies the trouble of overcoming the anticommons.

Heller & Eisenberg, *supra* note 30, at 700. Courtney C. Scala, however, has recently shown how patents pools in the field of pharmacogenomics—by aggregating patent rights—can overcome the hypothesized transaction costs, facilitate greater innovation and bring new personalized medical products to market. Courtney C. Scala, *Making the Jump from Gene Pools to Patent Pools: How Patent Pools Can Facilitate the Development of Pharmacogenomics*, 41 CONN. L. REV. 1631, 1644–45 (2009). Scala extends the earlier reasoning of Sheila F. Anthony in so far as she claims that intellectual property rights and antitrust law are not neces-

the attributive biases of the participants[41] are the primary barriers to successful negotiations. A more recent study by Professors John P. Walsh, Wesley M. Cohen, and Charlene Cho shows that while access to knowledge inputs is largely unaffected by patents, patents do appear to restrict access to cell lines, rea-

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sarily at odds with one another once one understands how the underlying foundations for each domain dovetail. *Id.* at 1651; *see also* Sheila F. Anthony, *Antitrust and Intellectual Property Law: From Adversaries to Partners*, 28 AIPLA Q. J. 1, 7 (2000).

[40] With respect to the heterogeneous array of interests that may impede licensing efforts, the primary divide resides in the conflicting capacities and ends of public patent holding institutions (e.g., universities) and private patent holding institutions (e.g., private firms). Heller and Eisenberg write:

> For example, a politically accountable government agency . . . may further its public health mission by using its intellectual property rights to ensure widespread availability of new therapeutic products at reasonable prices. When [the U.S. National Institutes of Health] sought to establish its co-ownership of patent rights held by Burroughs-Wellcome on the use of azidothymidine (AZT) to treat the human immunodeficiency virus (HIV) . . . , its purpose was to lower the price of AZT and promote public health rather than simply to maximize its financial return. By contrast, a private firm is more likely to use intellectual property to maintain a lucrative product monopoly that rewards shareholders and funds future product development. . . . [In addition, u]niversities may be ill equipped to handle multiple transactions for acquiring licenses to use research tools. . . . Large corporations with substantial legal departments may have considerably greater resources for negotiating licenses on a case-by-case basis than public sector institutions or small start-up firms. This asymmetry may make it difficult to identify mutually advantageous cross-licensing arrangements.

Heller & Eisenberg, *supra* note 30, at 700; *see also* Stephen M. Maurer, *Inside the Anticommons: Academic Scientists' Struggle to Build a Commercially Self-Supporting Human Mutations Database, 1999-2001*, 35 RES. POL'Y 839, 853 (2006); Richard R. Nelson, *The Market Economy, and the Scientific Commons*, 33 RES. POL'Y 455, 464 (2004); Oliver E. Williamson, *The Economics of Organization: The Transaction Cost Approach*, 87 AM. J. SOC. 548, 568–69 (1981).

[41] With respect to the cognitive biases and the attributive biases of the participants as barriers to successful negotiations in biotechnology, Heller and Eisenberg write, "[w]e suspect that a [cognitive] bias is likely to cause owners of upstream biomedical research patents to overvalue their discoveries." Heller & Eisenberg, *supra* note 30, at 701. Attribution bias flows from a similar overestimation of value—and one tied to the scientific method itself. *Id.* Scientists must invest a significant amount of time and energy in developing, testing, and proving a hypothesis. As a result, Heller and Eisenberg write, scientists "systematically overvalue their assets and disparage the claims of their opponents when in competition with others . . . . [T]his bias can interfere with clear-headed bargaining, leading owners to overvalue their own patents, undervalue others' patents, and reject reasonable offers." *Id.*

gents, or unpublished information.[42] The authors found that the existence of patents in these three fairly broad knowledge domains diminish the vigorous pursuit of new research projects and scientific competition in related areas of inquiry.[43]

Professor Zhen Lei's work suggests that Heller and Eisenberg's vague proposition regarding the potentially "negative effects" of patents requires disaggregation.[44] Lei and others contend that: (1) scientists "do not [generally] encounter an anti-commons or a patent thicket;" and (2) scientists do, however, assert that "institutionally mandated contracts [material transfer agreements (MTAs)] put sand in the wheels of a lively system of intra-disciplinary exchange of research tools."[45] In line with Lei's disaggregation hypothesis, Ha Hoang and Frank T. Rothaermel found positive benefits of biotech-pharmaceutical firm alliances for small biotechnology firms and negative marginal results of biotech-pharmaceutical firm alliances for large pharmaceutical corporations.[46] The difference lay in the heterogeneity of interests.

It is important to recall that most of Heller and Eisenberg's original examples were purely hypothetical at the time of publication. While having done the spadework for this new field of inquiry regarding thicket effects in biomedical and biopharmaceutical research, Heller and Eisenberg provided little empirical data to support their thesis.[47] Even more surprising is that the academic foot

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42 John P. Walsh et al., *Where Excludability Matters: Material Versus Intellectual Property in Academic Biomedical Research*, 36 RES. POL'Y 1184, 1185 (2007).

43 *Id.*; *see also* ORG. FOR ECON. CO-OPERATION & DEV., GENETIC INVENTIONS, INTELLECTUAL PROPERTY RIGHTS AND LICENSING PRACTICES: EVIDENCE AND POLICY 50–51 (2002), *available at* www.oecd.org/dataoecd/42/21/2491084.pdf; Dianne Nicol & Jane Nielsen, *Patents and Medical Biotechnology: An Empirical Analysis of Issues Facing the Australian Industry*, at 53–54 (Ctr. for Law & Genetics, Occasional Paper No. 6, 2003); John P. Walsh et al., *View from the Bench: Patents and Material Transfers*, 309 SCI. 2002, 2002 (2005); Sadao Nagaoka, Presentation at the CISI/OECD/OEPM Conference on Research Use of Patented Inventions, *An Empirical Analysis of Patenting and Licensing Practices of Research Tools from three Perspectives*, (May 16, 2006) at 22, *available at* http://www.oecd.org/sti/scienceandtechnologypolicy/36816178.pdf.

44 Zhen Lei et al., *Patents Versus Patenting: Implications of Intellectual Property Protection for Biological Research*, 27 NATURE BIOTECHNOLOGY 36, 36 (2009) (reporting a survey revealing that scientists view the proliferation of different forms of intellectual patents to have a negative effect on research).

45 *Id.*

46 Ha Hoang & Frank T. Rothaermel, *The Effect of General and Partner-Specific Alliance Experience on Joint R&D Project Performance*, 48 ACAD. MGMT. J. 332, 341–42 (2005).

47 Richard A. Epstein & Bruce N. Kuhlik, *Is There a Biomedical Anticommons?*, 27 REG. 54, 54 (2004); Fiona Murray & Scott Stern, *Do Formal Intellectual Property Rights Hinder the*

soldiers meant to serve Heller and Eisenberg's paradigm shift have been rather slow to enlist their services in the empirical battalions required to either prove or disprove Heller and Eisenberg's bold—and intuitively compelling—hypothesis. But slowness is not absence. Recent publications suggest that the gathering of the necessary empirical research to support or to qualify and to dispute the original thesis may be picking up speed. Mosoff's recent work on the U.S. sewing machine wars of the 1850s demonstrates that patent thickets have long existed, frustrate commercial development of new products, and are not limited to contemporary high tech innovations.[48]

With respect to high transaction costs acting as a barrier to successful negotiations in biotechnology, Maurer shows how 100 well-intentioned academics who (a) wished to create a worldwide depository for human mutations data and (b) received a $2.3 million corporate offer to construct such a depository, still found themselves unable to reach an agreement on whether to accept the offer because "most members could not afford the information costs needed to reach a decision."[49] Two other studies of the anticommons thesis in biomedical research cut in another direction. According to Walsh, Arora, and Cohen, little evidence supports the proposition that patent rights impede university research.[50] Another study, conducted by Jensen and Murray, reveals a very modest anticommons effect.[51] As matters stand, Heller and Eisenberg's thesis, while very heavily cited in the social science literature, has led to a comparatively small number of empirical studies about the presence and the causation of patent thickets surrounding the commercialization of complex pharmaceutical technologies.[52]

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*Free Flow of Scientific Knowledge? An Empirical Test of the Anti-Commons Hypothe*sis, 63 J. ECON. BEHAV. & ORG. 648, 648 (2007).

48 Adam Mossoff, *The Rise and Fall of the First American Patent Thicket: The Sewing Machine War of the 1850s*, 53 ARIZ. L. REV. 165, 211 (2011). Consistent with Shapiro's work, Mossoff challenges the conventional wisdom that problems raised by thickets are best resolved by "public-ordering regimes that limit property rights in patents." *Id.* at 165. Instead, Mossoff finds that creative technological, commercial, and legal ingenuities enable the patent holders to hack through an existing thicket and to help bring a remarkable product to market. *Id.*

49 Maurer, *supra* note 40, at 839.

50 John P. Walsh et al., *Working Through the Patent Problem*, 299 SCI. 1021, 1021 (2003).

51 *See* Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCI. 239, 240 (2005) (reporting that a moderate number of genes have fragmented ownership, which could potentially lead to increased costs in the licensing of genes); *see also* Murray & Stern, *supra* note 47, at 648.

52 Orsi & Coriat, *supra* note 26, at 1215–16; *see generally* Giovanni Abramo et al., *The Role of Information Asymmetry in the Market for University-Industry Research Collaboration*, 36 J.

We hope to reverse this trend. Our study provides new empirical evidence that patent thickets are indeed present in the pharmaceutical industry. The evidence of our investigation further demonstrates that the patent thicket effect grows stronger as the number of patents required for a downstream commercial product increases. In sum, the more patent licenses a seller must acquire to bring a product to market, the greater the patent thicket will be.

D. Patent Thickets in the Biopharmaceutical Industry

The present investigation focuses on the biopharmaceutical industry for three reasons. First, patent policies that stifle pharmaceutical development have always been controversial.[53] One should note that strong intellectual property protection for pharmaceuticals is a modern development—even in the most industrialized economies[54]—and is hotly contested in emerging markets.[55] Second, compared to patents in other industries, biotechnology patents are generally thought to be difficult to circumvent.[56] Third, the pharmaceutical industry engages in widespread partnerships, joint ventures, alliances, and cross-licensing.[57]

Given the size of the U.S. pharmaceutical industry,[58] the strength of U.S. patent laws,[59] the sophistication of U.S. development and licensing offices,[60] and

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TECH. TRANS. 84 (2011); John P. Walsh et al., *Effects of Research Tool Patents and Licensing on Biomedical Innovation*, *in* PATENTS IN THE KNOWLEDGE-BASED ECONOMY 285 (Wesley M. Cohen & Stephen A. Merrill eds., 2003).

53 Nicholas S. Argyres & Julia P. Liebeskind, *Privatizing the Intellectual Commons: Universities and the Commercialization of Biotechnology*, 35 J. ECON. BEHAV. & ORG. 427, 450–51 (1998); Elliot A. Fishman, MIT Patent Policy, 1932 – 1946: Historical Precedents in University-Industry Technology Transfer (1996) (unpublished Ph.D. dissertation, University of Pennsylvania) (on file with the University of Pennsylvania).

54 Sprague & Woolman, *supra* note 4, at 351.

55 *See* Woolman & Sprague, *supra* note 4, at 346–47, 358–60; *see also* Anna B. Emilio, *Tripping over TRIPS and the Global HIV/AIDS Epidemic: Legislation and Political Decisions in Brazil and the United States*, 28 J. CONTEMP. HEALTH L. & POL'Y 57, 84 (2011); Caroline Manne, Note, *Pharmaceutical Patent Protection and TRIPS: The Countries That Cried Wolf and Why Defining "National Emergency" Will Save Them from Themselves*, 42 GEO. WASH. INT'L L. REV. 349, 378–79 (2010).

56 Cohen et al., *supra* note 18, at 1184–85.

57 Epstein & Kuhlik, *supra* note 47, at 54–55; s*ee generally* Rebecca Henderson et al., *The Pharmaceutical Industry and the Revolution in Molecular Biology: Interactions Among Scientific, Institutional, and Organizational Change*, *in* THE SOURCES OF INDUSTRIAL LEADERSHIP 267 (David C. Mowery & Richard R. Nelson eds., 1998).

58 Matthew Herper & Peter Kang, *The World's Ten Best Selling Drugs*, FORBES (Mar. 22, 2006, 6:00 AM), http://www.forbes.com/2006/03/21/pfizer-merck-amgen-cx_mh_pk_0321topdrugs.html.

the vast networks of private and public partnerships,[61] one might think that, with such vast resources, a strong yet supple legal regime and an ongoing commitment to collective action would accelerate the production of new drugs.[62] Yet it would appear that transaction costs, heterogeneous interests, cognitive biases, and attributive biases often block the commercialization of new drugs.[63] We begin our analysis by demonstrating that patent thickets persist in otherwise hospitable environments for biomedical research and commercial pharmaceutical production.

III. THEORY DEVELOPMENT AND HYPOTHESIS

We test for the existence and influence of a patent thicket in the biopharmaceutical industry by analyzing the extent to which patent licenses were present in the top 200 selling drugs in the U.S. in 2007. Our analysis demonstrates that the thicket effect first becomes significant when a potential seller must acquire a license from two or more patent owners in order to create a downstream, commercially viable product. The effect becomes progressively more pronounced as more patent owners become involved. Once the potential

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59 Adam B. Jaffe, *The U.S. Patent System in Transition: Policy Innovation and the Innovation Process*, 29 RES. POL'Y 531, 554 (2000).

60 *See generally* Tony Calabrese et al., *Canadian Biotechnology Start-Ups, 1991-1997: The Role of Incumbents' Patents and Strategic Alliances in Controlling Competition*, 29 SOC. SCI. RES. 503 (2000) (Although strong patent regimes can make downstream commercial viability of a biotechnology product difficult in both the United States and Canada, the authors demonstrate how start-ups can overcome hurdles associated with development of new drugs within strong patent regimes through (a) early establishment of alliances that (b) allow for the sharing of critical information in a manner which (c) allows for greater learning and decreased risk for all parties).

61 *See generally* Weijan Shan et al., *Interfirm Cooperation and Startup Innovation in the Biotechnology Industry*, 15 STRATEGIC MGMT. J. 387 (1994) (showing that interfirm cooperation enhances innovation, though the reverse hypothesis, that innovation enhances interfirm cooperation is not true).

62 Sometimes the uncertainty of patent law itself stifles innovation in the biopharmaceutical industry. *See* Christopher M. Holman, *Unpredictability in Patent Law and Its Effect on Pharmaceutical Innovation*, 76 MO. L. REV. 645, 650–51 (2011). *But see* Harry Surden, *Efficient Uncertainty in Patent Interpretation*, 68 WASH. & LEE L. REV. 1737, 1743 (2011) (Despite the strength of the US patent regime, the variability of FDA approval for a drug, difference in judicial recognition as to whether a patent obtains in a given set of circumstances, and the success that the producers of generic drugs have had despite the presence of an applicable patent, dampens enthusiasm for new research and development projects that would bring much needed pharmaceuticals to market).

63 Heller & Eisenberg, *supra* note 30, at 698.

seller is obliged to acquire a license from four or more patent owners, negotiating the necessary licenses becomes virtually impossible. In short, our analysis suggests that fewer novel drugs will be manufactured as the number of necessary licenses per drug increases.

A. The Thicket Effect on the Probability of a Drug's Commercialization

To quantify the thicket effect, we start by envisioning a hypothetical drug manufacturer or seller that has developed a drug and would bring it to market but for the fact that the production of the drug requires active pharmaceutical ingredients covered by one or more patents owned by other parties. In other words, we assume a drug exists that is commercially viable and that would get to market but for another patent holder blocking its development through an injunction or the threat thereof. To market the drug, the seller must secure a license from every party that owns one or more of the necessary patents. To determine whether there is a thicket effect, we must first identify what consequences, if any, the number of apposite patents and the number of apposite patent holders will have on the probability of the drug being brought to market.

To do this, we made a number of initial, critical, and perhaps controversial assumptions. First, we do not consider the effect of patents owned by a potential drug seller itself because those patents obviously do not require a license and thus do not impair the commercialization efforts of the owner. Second, we assume that the difficulty of negotiating a license with a party is independent of the number of patents owned by that party. We make this assumption because companies typically enter into a single license agreement with drug sellers that cover all relevant patents. Companies rarely negotiate separate agreements for each patent. Given these initial assumptions, the probability that a drug will be brought to market is a function of the total number of patentees (not counting the drug seller itself).[64] Of course, as we will discuss in the Re-

[64] We recognize that our analysis rests upon a number of assumptions that might warrant further scrutiny in a future paper. However, we believe that the data set employed will support the proposition that patent thickets exist in complex biopharmaceutical technologies. Several alternative but unanalyzed hypotheses have been proffered by others. They claim that the failure of some complex biopharmaceutical technologies to produce a commercially viable drug may be (a) a function of additional FDA approval hurdles, (b) that companies self-select out of the process of trying to bring a drug to market because of market size or (c) the cost of clinical protocols are entirely speculative. The fact that multiple barriers (in different environments) may exist with respect to bringing many efficacious drugs to market does not entail the proposition that one cannot say something meaningful about some of those barriers. Careful academics, rightly concerned with the built-in skepticism of the scientific community

search Design section below, the available public data reflects only those drugs that actually made it to market and the parties that owned the patents covering each drug. We have been unable to obtain data representing drugs that might have made it to market but for a large number of patent holders and the consequent thicket effects because corporations do not generally disseminate information regarding their inability to secure all the requisite licenses to bring a drug to market. To reflect the actual data, our theory must represent the probability that a given drug meets two criteria: (1) before licensing activities occurred, it was covered by patents owned by N patentees ("patent owners"), and (2) the drug seller succeeded in negotiating the requisite N licenses in order to manufacture the product. Only drugs satisfying both criteria will have made it to market.

How does one express that probability quantitatively? We reason that if (a) the drug is commercially viable; (b) no outside licenses are necessary; and (c) no other factors hinder marketability, then the probability of the drug being brought to market is 1. If licenses must be secured from a large number of patent owners, then the drug seller will experience thicket effects that make effective negotiation virtually impossible. Expressed quantitatively, the probability of a drug being brought to market (P_{Mkt}) tends toward 0 for drugs requiring licenses from a large number of patent owners. Intermediate cases exist. Where the new drug requires the acquisition of some patents, but not an excessive number of patents, the probability of successfully negotiating all necessary licenses is somewhere between 0 and 1.[65] We have, therefore, created a model that fits the above three assumptions: first, a probability of 1 if there are no external patent holders; second, a probability of 0 if a large number of external patent holders exist; and third, a probability between 0 and 1 if there are no more than a few patent holders. The vagaries of human behavior—personality clashes, bluffing, discouragement, and obstinacies, just to name a few—introduce externalities that make it difficult, if not impossible, to construct a precise model. We bracketed such human behavior and propose instead a sim-

within which they operate, very rarely set about trying to offer a theory of everything. Our aim is, therefore, quite modest. Our goal is to establish an evidentiary basis, using readily available public data, to support the hypothesis that patent thickets can form in response to complex biopharmaceutical technologies. We do not contend that complex biopharmaceutical technologies might not also face other barriers in getting to market. (However, we leave others to identify those barriers and provide adequate support to support their hypotheses about the insuperability of those impediments.)

65 As the Histogram in Figure 3 and the Strong Thicket graph in Figure 6 both show, the range of licenses in our data set runs from 0 (where the probability of marketability is 1) to 4 (where the probability of marketability falls to 0).

plified, approximate model for P_{Mkt} as represented by the following piecewise linear function:

For $N < N_T$, $P_{Mkt} = 1$; (Equation 1(a))
For $N > N_T$, $P_{Mkt} = 1 - M (N - N_T)$. (Equation 1(b))

Where:

P_{Mkt} is the probability of all necessary licenses being negotiated, and equivalently, the probability that an otherwise commercially viable drug will be brought to market;

N is the number of patent owners covering the drug other than the seller;

N_T is a threshold number of patent owners above which the probability of bringing the drug to market drops rapidly; and

M is the rate at which P_{Mkt} diminishes for $N > N_T$.

B. Strong Patent Thickets in Complex Biopharmaceutical Technologies

Strong thicket analysis takes into consideration how transaction costs, heterogeneous interests, cognitive biases, and attributive biases can impede commercialization efforts. These externalities can interfere with the behavior of those actors who control the licensing process and cause them to act in a manner that compromises economically rational conduct. A strong thicket model does *not* assume that if a license needs to be secured, then it will be secured irrespective of the amount of bargaining.

How is this last proposition stated mathematically? As we discussed above, to bring a drug to market, the seller must obtain exactly one license from each patent owner (not counting the drug seller itself). Under this assumption, for any given drug that actually made it to market, we know that all necessary licenses were secured.[66] Thus, for any drug known to be on the market, the probability that the drug is covered by N licenses equals the probability that patents owned by N patentees other than the seller cover it. For each such drug, two conditions must be satisfied: (1) before any license negotiations occurred, there must have been N patentees from whom licenses were required, and (2) at some point, licensing agreements were successfully negotiated with all N patentees. The probability of simultaneously satisfying both criteria is the product

[66] Necessary licenses encompass only licenses for "blocking patents" of which the drug seller is aware. We do not expect unknown patents to affect the seller's decision-making.

of their respective probabilities for each N: in other words, $P = P_L P_{Mkt}$. Equivalently:

$P = P_1^N$ for $N < N_T$; and (Equation 2(a))
$P = P_1^N (1 - M (N - N_T))$ for $N > N_T$. (Equation 2(b))

Where:

N is the number of patent owners (other than the seller) whose patents cover the drug (or alternatively stated, the number of licenses required to manufacture the drug);

P_1 is the probability that a given, unknown drug is covered by a patent (or patents) owned by a single patentee;

N_T is a threshold number of patentees above which the probability of bringing the drug to market drops rapidly; and

M is the rate at which P_{Mkt} diminishes for $N > N_T$.

In these models, the sum of all the probabilities under all N values must be 1. This insight allows us to express the value of $P_{N=0}$ as follows:

$$1 - \sum_{N=1}^{\infty} P$$

It follows that if $N_T > 1$, then P_1 appears as a two-segmented piecewise function: the strong thicket model.

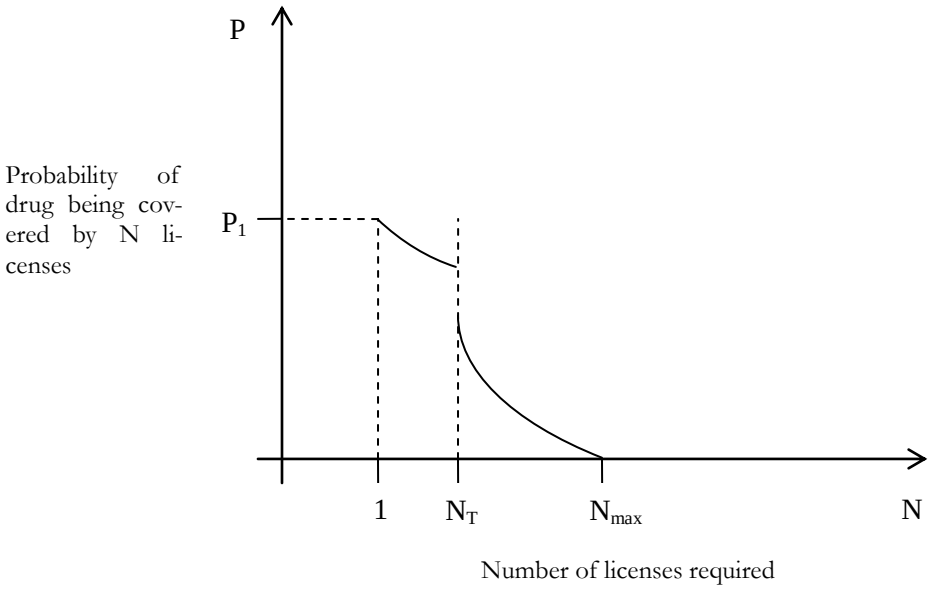

Figure 1: Strong Thicket where $N_T > 1$

But if $N_T < 1$, then P_1 appears as illustrated in Figure 2. For this function, we denominate the second strong thicket model. Note that for each model we only consider the region where $N \geq 1$ because the value of P where $N<1$ would simply be $P_{N=0}$ as expressed in Equation 3, below.

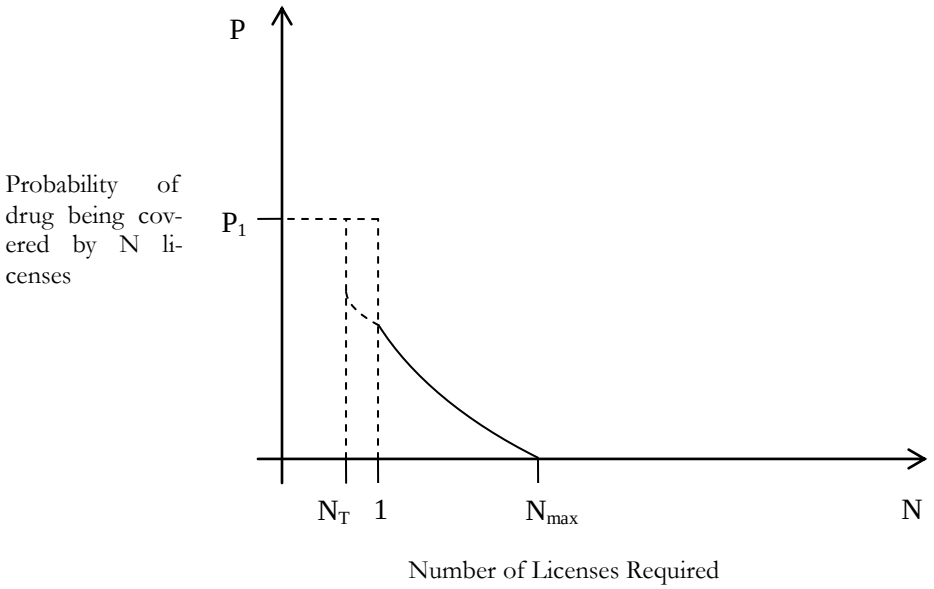

Figure 2: Strong Thicket where $N_T < 1$

1. Preview of Data and Hypothesis

We assembled a proprietary database of licensed patents for each of the top 200 selling drugs in the U.S. in 2007. We then combed the records and counted how many licensed patents comprise each of the 200 drugs. The presence or absence of patent licenses in the top 200 selling drugs in the U.S. provides a picture of thicket effects that are either (a) so strong as to impede commercialization or (b) so sufficiently weak that licensing managers were able to hack their way through. In order to visualize the thicket environment, we created a histogram shown in Figure 3 below.

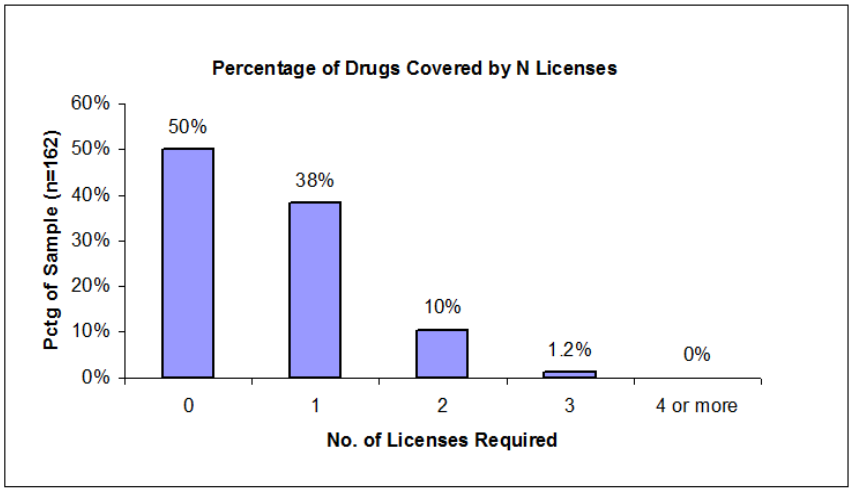

Figure 3

After creating this histogram, we immediately recognized that the number of top-selling drugs fell off dramatically after just two patent licenses were required from other parties. Following the patent thicket hypotheses of Heller and Eisenberg, we theorized that the precipitous fall off was caused by factors they had originally tendered: exponentially increasing transaction costs, heterogeneous interests, cognitive biases, and attributive biases. However, it is once again important to note that our data and methodology allow us to infer only that the strong thicket effects exist. The data does not speak to the specific underlying causes for any given strong thicket.

Nonetheless, we are now in a position to propose five testable hypotheses that measure and characterize the thicket in biomedical research. These hypotheses are as follows:

H1: Due to thicket effects and licensing requirements, there will be more top-selling drugs requiring 0 patent licenses than drugs requiring 1 or more patent licenses.

H2: Due to thicket effects and licensing requirements, there will be more top-selling drugs requiring 1 patent license than drugs requiring 2 or more patent licenses.

H3: Due to thicket effects and licensing requirements, there will be more top-selling drugs requiring 2 patent licenses than drugs requiring 3 or more patent licenses.

H4: Due to thicket effects, there will be very few top-selling drugs requiring 3 patent licenses available in the marketplace.

H5: Due to thicket effects, there will be no top-selling drugs requiring 4 or more patent licenses available in the marketplace.

The histogram above (Figure 3) partially confirms these hypotheses. This observation would be the end of the analysis but for the theoretical model developed above. The model allows us to quantitatively test for strong thicket effects on a probabilistic basis grounded upon the number of licenses required. By fitting a curve to the known distribution probabilities of pharmaceutical thickets (as shown in Figure 2), we can derive specific parameters for Equation 3:

$$P = P_1^N (1 - M (N - N_T)) \text{ for } N > N_T \qquad \text{(Equation 3)}$$

This equation represents the probability of commercialization. We, therefore, propose a sixth testable hypothesis.

H6: Assuming the 200 top-selling drugs in the U.S. in 2007 reflect patent thicket dynamics in biomedical research, the probability of negotiating all necessary licenses is a decaying exponential function of the number of licenses. Where the number of required licenses rise above the aforementioned threshold, the probability can be approximated by the same decaying exponential function multiplied by a steeply declining linear function. Furthermore, parameters for these functions may be derived and usefully applied.

2. Research Design: Data Collection & Experimental Method

a. Raw Data

In order to test the sixth hypothesis, we needed to acquire raw data on licensing transactions in the biopharmaceutical industry. Because no such database currently exists, we compiled a suitable data set. First, we built a database that associated top-selling drugs with their patent owners. The list of the top 200 selling drugs in the U.S. for 2007 is drawn from the Verispan Vona survey data for annual industry drug sales.[67] Second, we cross-referenced each drug with its constituent patents using a file from the United States Food & Drug

[67] *Pharmaceutical Sales 2007*, DRUGS.COM, http://www.drugs.com/top200_2007.html (last visited Nov. 6, 2012).

Administration ("FDA") called the FDA Orange Book.[68] Among other things, the Orange Book identifies all patents that cover each listed drug.[69]

Although the list of patents in the Orange Book is only as complete as the information drug sellers provide to the FDA, a drug seller has a strong incentive to maintain accurate patent information because of a law commonly referred to as the "marking statute".[70] In pertinent part, the statute provides that a patentee can lose its back damages if it fails to mark a product sold under the patent with the patent number.[71] This requirement to mark products applies even if it is a patent owner's licensees, not the patent owner itself, selling the product.[72] A drug covered by one or more patents will be marked with those patent numbers whether it is sold by the patentee or by a licensee.

For each patent number associated with a particular drug, we determined ownership rights using assignment data from the United States Patent & Trademark Office ("USPTO").[73] While companies are not legally required to report post-issue assignment data, we postulate that most patentees maintain current records with the USPTO because they have a strong incentive to do so. If they do not and the original owner subsequently attempts to sell the patent to another party, they risk having to contest ownership rights.[74] Logging current assignment information with the USPTO is considered prudent and customary industry practice.[75]

Based on the Orange Book data and the USPTO assignment records, we built a table of patent information for the top 200 drugs sold in the U.S. in 2007. Each row of the table identifies a drug, the patents covering it, the owners of those patents, and the number of companies (other than the seller itself) that own one or more of the listed patents. When determining the number of patent owners, we treated parent companies, subsidiaries, and affiliates as a single company because a drug seller would not need to conduct separate negotiations with related companies.

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68 *The Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/cder/ob/default.htm (last visited Nov. 6, 2012).

69 *Id.*

70 35 U.S.C. § 287(a) (2006).

71 *Id.*

72 Nike, Inc. v. Wal-Mart Stores, Inc., 138 F.3d 1437, 1446–47 (Fed. Cir. 1998).

73 Assignment data from the USPTO can be found at *Patent Assignment Query Menu*, USPTO, http://assignments.uspto.gov/assignments/?db=pat (last visited Nov. 6, 2012).

74 69 C.J.S. *Patents* § 446 (2012).

75 Pauline Stevens, *Security Interests in Patent and Patent Applications?*, 6 U. PITT. J. TECH. L. & POL'Y 2, 2 (2005).

Our derivation of licensing information warrants an explanation. License information is not available directly from any database. In many instances, companies do not disclose licensing transactions. However, we constructed reasonable inferences regarding the existence of a license by determining whether the drug manufacturer (or its subsidiaries) was assigned all the patents required to manufacture a drug. If any drug was covered by a patent not registered with the manufacturer (or its subsidiaries), then a license must exist. In other words, another party would have had to enter into a licensing agreement for a patent in order for the manufacturer to bring the commercially viable product to market. This information is recorded in the table as a separate column. A sample of five of the table's 200 rows is shown in Figure 4 below, and a reproduction of the entire table is to be found in the Appendix.

Row 1 of Figure 4 shows data for Lipitor, a best-selling drug; the number of patents upon which this drug relies (5); U.S. sales in billions of dollars in 2007 ($6.165); the manufacturer of the drug (Pfizer); the number of patent owners (or "assignees") per drug of the various patents upon which the drug relies (1); and the number of licenses as reflected by USPTO data.

Drug Name	# of Patents	US Sales ($US Billions)	Manufacturer	# of Assignees	# of Licenses
Lipitor	5	6.145	Pfizer	1	1
Nexium	13	4.355	Astrazeneca	3	2
Advair	5	3.390	GlaxoSmithKline	2	1
Prevacid	6	3.315	TapPharm	2	2
Plavix	4	3.082	SanofiAventis	2	1

Figure 4

b. Descriptive Statistics

The following table provides descriptive statistics about drug sales by the U.S. pharmaceutical industry. The table summarizes information in the Appendix. We note that the median number of patents covering each drug was roughly three per drug while the median number of patents pharmaceutical companies licensed was one. The highest number of licenses was three, and the most frequent number of licenses was zero. These numbers provide further quantitative evidence of a strong thicket effect. Were patents to be licensed more easily, the highest number would be far greater than three.

We also note that out of the top 200 drugs sold in the U.S. in 2007, thirty-eight (19%) had no currently enforceable patents associated with them. Whether patents had never covered them, or the patents covering them have now expired, these drugs are susceptible to competition from generic drug manufacturers and tend to sell at much lower margins than drugs covered by patents still in force. For drugs not covered by any unexpired patents, no thicket effects exist because it is not necessary to procure patent licenses. We therefore eliminated them from our study.

Descriptive Statistics of the 200 Top Selling Drugs

	Patents per Drug	2007 Sales – US $ Millions	Patents Licensed
total	636	130,456	102
average	3.93	652	0.51
median	3.00	373	1
standard deviation	3.93	777	0.72
high value	16	6,165	3
low value	1	144	0
mode	2	293	0

Figure 5

c. Experimental Method

As discussed in the hypothesis section above, we developed an equation designed to identify the presence of a strong thicket. Note that this strong thicket equation has two regions, each with a different form, depending on whether the value of N is greater than or less than N_T.

Strong thicket: $P = P_1^N$ for $N < N_T$; and
$P = P_1^N (1 – M (N – N_T))$ for $N > N_T$.

For the strong thicket equation, we calculated the frequency distribution of the top selling drugs having 0, 1, 2, 3, and 4 licenses. The results are reflected in the histogram above (Figure 3). Then we wrote a custom software program to regress these data points with the equation for the strong thicket. The resulting parameters, P_1, N_T and M were written to a file. We confirmed the fit

of these parameters by using a chi-square test with two degrees of freedom for each function.

IV. EMPIRICAL RESULTS AND DISCUSSION

The regression of the strong thicket function yielded the following parameter values:

$P_1 = 0.4136$
$N_T = 0.7656$
$M = 0.3447$

The results are presented graphically in Figure 6 below.

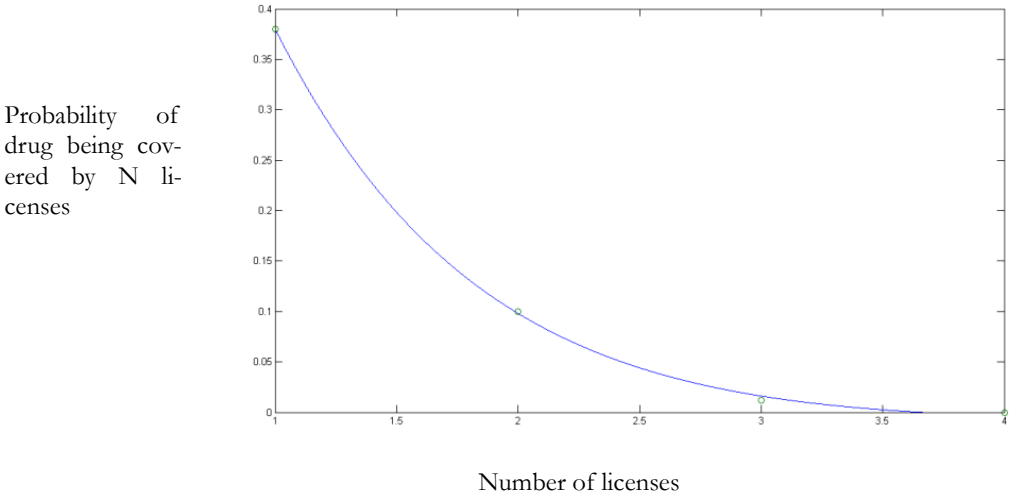

Figure 6: Strong Thicket

The salient observation is that the strong thicket curve intersects the zero probability line by the time a fourth license is required to commercialize a drug. In other words, virtually no possibility exists for a licensing manager to negotiate successfully with four separate patent owners. This conclusion provides compelling evidence for the presence of a patent thicket in complex biopharmaceutical technologies.

V. CONCLUSIONS, IMPLICATIONS & FUTURE RESEARCH AGENDAS

Rights to a unified patent estate, not just ownership of one patent, are usually necessary to manufacture and market a new drug. Our data shows that most commercialized drugs rely on two or more patents for their production process, formulation, or delivery system. Whenever a biopharmaceutical firm lacks all the requisite patent rights, it must negotiate licenses with other patentees. This requirement may explain the extensive number of intercompany partnerships, collaborations, and joint ventures in biotechnology.[76] Our conclusions prompt two further questions. Should the industry generally sanction flexible patent licensing transactions? Or, should the industry maintain a more rigid, permanent assignment of patent rights?

Our study suggests that biopharmaceutical patents are more often assigned than licensed. In fact, our data compilation in the Appendix reveals only 102 patent licensing agreements among the 200 leading pharmaceuticals. Given the extent of inter-firm cooperation, one would expect numerous licenses per drug. We found, however, that, on average, only one out of every two drugs relies on licensed-in patents. While approximately 50% of our sample depended on patents licensed from three patentees or less, there are no documented cases of drugs relying on rights from four or more patentees (Figure 6).

The scarce number of licensing transactions and dearth of multiple-party transactions lends credence to the anticommons hypothesis of Heller and Eisenberg—that exponentially increasing transaction costs, heterogeneous interests, cognitive biases, and attributive biases impede innovation in biomedicine. Our theoretical model and empirical results support the existence of patent thickets with respect to the commercialization of drugs that require complex—as opposed to discrete—biopharmaceutical technologies. We quantify those thicket effects as follows: (1) it first appears significantly when the seller must acquire a license from two or more patent owners; (2) it becomes quite pronounced when the seller must acquire a license from three or more patent owners; and (3) where four or more patent owners exist, the thicket effect makes negotiating the necessary licenses virtually impossible. We derived mathematically parameters for the sharp drop off between steps (1) and (3) above.

Numerous opportunities exist to extend this initial study. First, our data was sampled at the level of the patent license. We could not explore the underlying cause of any given patent thicket—despite new methods for their objective identification—because most of the information regarding the failure to secure a successful patent estate is rarely, if ever, made public. Are transaction costs,

[76] Bessan, *supra* note 21, at 19–20; Mossoff, *supra* note 48, at 195–96.

heterogeneous interests, cognitive biases, or attributive biases the greatest impediments to complex biopharmaceutical technology innovation? Or does (a) the onerous nature of FDA approval, (b) comparatively small potential markets for viable drugs, or (c) opting out (for myriad reasons) by companies that might otherwise bring a complex biopharmaceutical technology to market, provide complimentary, though not contradictory, explanations for this peculiar form of market failure? Second, our analysis benefitted from the ease by which we secured publicly accessible data. As a result, we have looked only at the U.S. biopharmaceutical industry. To what extent do thickets in complex biopharmaceutical technologies interfere with patent licensing activity and downstream commercialization of drugs in other parts of world? A study conducted in South Africa or Brazil might reveal a different pattern: this pattern would reflect a strong intellectual property rights regime that governs a somewhat less fecund biopharmaceutical research and development environment.[77] One might expect diminished thicket effects in countries governed by more relaxed patent laws and compulsory licensing. France is an excellent example of such a jurisdiction. But for the comparison to be meaningful, one must simultaneously ask whether such jurisdictions produced significant amounts of commercially viable products within the domain of complex biopharmaceutical technologies. Finally, our study derived particular strong thicket functions and their parameters from relatively recent data. Future research may reveal whether our model is robust enough to be used for predictive purposes.

Certain policy implications flow from our conclusion that strong patent thickets exist with respect to complex biopharmaceutical technologies. In recent years, there have been movements to reform the patent systems around the world and unwind some of the strength patent owners secured during the end of the last millennium.[78] While a rigorously enforced patent system may optimize social welfare,[79] such a patent system presupposes that economically rational

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77 Sprague & Woolman, *supra* note 4, at 364–69.

78 *Id.* at 358–62.

79 *See generally* Kenneth Arrow, *Economic Welfare and the Allocation of Resources for Invention*, *in* THE RATE AND DIRECTION OF INVENTIVE ACTIVITY AND SOCIAL FACTORS 609 (1962) (explaining that optimality in resource allocation can be inhibited by uncertainty); Bronwyn H. Hall & Rosemarie H. Ziedonis, *The Patent Paradox Revisited: An Empirical Study of Patenting in the U.S. Semiconductor Industry, 1979-1995*, 32 RAND J. ECON. 101, 125 (2007) (noting that while strong patent regimes may facilitate innovation, they may actually spawn 'patent portfolio races' that actually work to inhibit innovation in the semi-conductor industry); Edwin Mansfield, *Patents and Innovation: An Empirical Study*, 32 MGMT. SCI. 173 (1986) (finding that roughly 60% of pharmaceutical innovations required patent protection, while only 14% of other forms of innovation across all other industries required the same degree of legal shelter); Roberto Mazzoleni & Richard R. Nelson, *The Benefits and Costs of*

actors can and will pre-negotiate agreements to resolve ownership of IP rights of downstream products.[80] The observed failure of patent holders to pre-negotiate where four or more licenses are required suggests that market externalities create strong thickets that no licensing manger in the biopharmaceutical industry will be able to overcome.[81] As we noted at the outset, most socially desirable drugs do not flow from discrete biopharmaceutical technologies that do not require negotiations. As a result, anyone concerned with the interaction of patents, innovation and socially desirable drugs ought to turn their attention to the vexed question of how we can best overcome the various obstacles to the commercial viability present in drugs derived from complex pharmaceutical technologies. A new and more nuanced regulatory regime can, and should, be designed to nudge patent holders and manufacturers into overcoming the various biases that create patent thickets and thereby prevent commercially viable drugs based upon complex biopharmaceutical technologies from being brought to market.[82]

Strong Patent Protection: A Contribution to the Current Debate, 27 RES. POL'Y 273, 280 (1998) (while not denying the proposition that a healthy patent regime was necessary to stimulate innovation, the authors caution that the then existing pressure to strengthen the existing regime might hamper or hinder technological and economic progress).

80 *See generally* Isabelle Huys et al., *Legal Uncertainty in the Area of Genetic Diagnostic Testing*, 27 NATURE BIOTECH. 903 (2009) (examining one factor—determination of patent scope—that adds uncertainty to the negotiation process).

81 Douglas G. Lichtman, *Patent Holdouts in the Standard-Setting Process* 7–8 (U. Chi. Inst. Law & Econ., Working Paper No. 292, 2006), *available at* http://www.law.uchicago.edu/files/files/292.pdf.

82 RICHARD H. THALER & CASS R. SUNSTEIN, NUDGE: IMPROVING DECISIONS ABOUT HEALTH, WEALTH, & HAPPINESS (2008) (in their work on choice architecture, the authors show how, after running multiple experiments on the owners of biotechonology patents for commercially viable drugs, a more efficient regulatory regime for pharmaceuticals can be devised using information regarding the adaptive preferences of the patent holders themselves: in sum, the participants in multiple licensing scenarios provide the insight necessary to create a legal environment in which the owners of patents for commercially viable drugs in complex biopharmaceutical technologies are more readily nudged toward reaching the necessary licensing agreements to bring the drug to market); Dan L. Burk & Mark A. Lemly, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1682–83 (2003); Geertrui Van Overwalle, *Policy Levers Tailoring Patent Law to Biotechnology: Comparing U.S. and European Approaches*, 1 U.C. IRVINE L. REV. 435, 517 (2011); Katherine J. Strandburg, *What Does the Public Get? Experimental Use and the Patent Bargain*, 2004 WIS. L. REV. 81, 124–25 (2004).

VI. APPENDIX: TABLE OF TOP SELLING 200 DRUGS IN 2007 IN UNITED STATES

No.	Drug Name	No. of Patents	US Sales ($US Billion)	Manufacturer	No. of Assignees	No. of Licenses
1	Lipitor	5	6.165	PFIZER	1	1
2	Nexium	13	4.355	ASTRAZENECA	3	2
3	Advair Diskus	5	3.39	GLAXOSMITHKLINE	2	1
4	Prevacid	6	3.315	TAP PHARM	2	2
5	Plavix	4	3.082	SANOFI AVENTIS US	2	1
6	Singulair	1	2.863	MERCK	1	0
7	Seroquel	2	2.518	ASTRAZENECA	1	0
8	Effexor XR	7	2.464	WYETH PHARMS INC	1	0
9	Lexapro	1	2.304	FOREST LABS	1	1
10	Actos	11	2.229	TAKEDA PHARMS NA	1	0
11	Protonix	1	2.136	WYETH PHARMS INC	1	1
12	Vytorin	3	1.938	MSP SINGAPORE	1	1
13	Topamax	5	1.837	Ortho-McNeil Pharmaceutical	3	2
14	Risperdal	16	1.79	ORTHO MCNEIL JANSSEN	2	2
15	Abilify	2	1.781	OTSUKA	2	1
16	Cymbalta	3	1.732	LILLY	1	0
17	Lamictal	2	1.717	GLAXOSMITHKLINE	1	1
18	Zyprexa	1	1.579	LILLY	1	0
19	Levaquin	1	1.433	ORTHO MCNEIL JANSSEN	1	1
20	Celebrex	4	1.416	GD SEARLE	1	0
21	Zetia	3	1.405	MSP SINGAPORE	1	1
22	Valtrex	3	1.395	GLAXOSMITHKLINE	2	1
23	Crestor	3	1.367	IPR	2	2
24	Fosamax	5	1.355	MERCK	1	0
25	Zyrtec	1	1.302	MCNEIL CONSUMER	1	1

26	Lantus	2	1.302	SANOFI AVENTIS US	1	0
27	Adderall XR	2	1.288	SHIRE	1	0
28	Diovan	2	1.117	NOVARTIS	1	0
29	Avandia	4	1.11	SB PHARMCO	1	0
30	Tricor	8	1.106	ABBOTT	3	3
31	Aciphex	2	1.099	EISAI MEDCL RES	1	0
32	Diovan HCT	2	1.051	NOVARTIS	1	0
33	OxyContin	4	1.043	PURDUE PHARMA LP	1	0
34	Concerta	2	1.03	ORTHO MCNEIL JANSSEN	1	1
35	Coreg	4	1.013	SMITHKLINE BEECHAM	2	1
36	Flomax	1	1.002	BOEHRINGER INGELHEIM	1	1
37	Lyrica(partners in deal	3	1	CP PHARMS	2	2
38	Wellbutrin XL	2	0.992	SMITHKLINE BEECHAM	1	1
39	Aricept	1	0.983	EISAI MEDCL RES	1	0
40	Imitrex Oral		0.95	GLAXOSMITHKLINE	patent expired	
41	Ambien	1	0.92	SANOFI AVENTIS US	1	0
42	Lotrel	1	0.908	NOVARTIS	1	0
43	Nasonex	3	0.892	SCHERING PLOUGH	1	0
44	Toprol XL		0.888	NOVARTIS	patent expired	
45	Ambien CR	1	0.876	SANOFI AVENTIS US	1	0
46	Enbrel		0.874	AMGEN and WYETH PHARM	patent expired	
47	Spiriva	7	0.868	BOEHRINGER INGELHEIM	1	0
48	Viagra	2	0.824	PFIZER IRELAND	1	0
49	Lidoderm	5	0.808	TEIKOKU PHARMA USA	2	1

50	Actonel	7	0.791	PROCTER AND GAMBLE	2	1
51	Chantix	3	0.764	PFIZER INC	1	0
52	Norvasc		0.749	PFIZER	patent expired	
53	Lovenox	2	0.746	SANOFI AVENTIS US	1	1
54	Provigil	3	0.744	CEPHALON	1	0
55	Lunesta	4	0.712	SEPRACOR	1	0
56	Altace	2	0.71	KING PHARMS	1	1
57	Keppra	1	0.708	UCB INC	1	0
58	Geodon Oral(no info)	4	0.665	PFIZER	1	0
59	Cozaar	4	0.652	MERCK	1	1
60	Detrol LA	4	0.635	DETROL LA PHARMACIA AND UPJOHN	2	1
61	Atripla	15	0.617	GILEAD	3	2
62	Truvada	10	0.606	GILEAD	2	1
63	CellCept		0.599	ROCHE PALO	patent expired	
64	Pulmicort Respules	2	0.592	ASTRAZENECA	1	0
65	Humalog	4	0.592	LILLY	1	0
66	Depakote ER	9	0.577	ABBOTT	1	0
67	Depakote	2	0.573	ABBOTT	1	0
68	Premarin Tabs		0.557	WYETH PHARMS INC	patent expired	
69	Synthroid		0.547	ABBOTT	patent expired	
70	Niaspan	8	0.546	ABBOTT	1	1
71	Byetta	6	0.541	AMYLIN	2	1
72	Budeprion XL		0.537	TEVA PHARMA	patent expired	
73	Strattera	1	0.535	LILLY	1	0
74	Combivent	1	0.534	BOEHRINGER INGELHEIM	1	0
75	Trileptal	1	0.532	NOVARTIS	1	0

76	Yasmin 28	3	0.528	BAYER HLTHCARE	1	0
77	Flovent HFA	9	0.521	GLAXO GRP LTD	2	2
78	Skelaxin	2	0.517	KING PHARMS	1	0
79	Prograf		0.515	ASTELLAS	patent expired	
80	Arimidex	2	0.506	ASTRAZENECA	1	0
81	Evista	12	0.503	LILLY	1	0
82	Hyzaar	3	0.499	MERCK	1	1
83	Namenda	1	0.489	FOREST LABS	1	1
84	Januvia	6	0.471	MERCK CO INC	3	2
85	Humira		0.462	ABBOTT PHARMACEUTICALS	patent expired	
86	Cialis	5	0.453	LILLY	2	1
87	Reyataz	2	0.438	BRISTOL MYERS SQUIBB	2	1
88	Xalatan	4	0.43	PHARMACIA AND UPJOHN	1	0
89	Omnicef		0.429	ABBOTT	patent expired	
90	Avelox	4	0.424	BAYER PHARMS	1	0
91	ProAir HFA	4	0.421	TEVA GLOBAL	1	1
92	Asacol	2	0.42	PROCTER AND GAMBLE	1	1
93	Benicar HCT	2	0.414	DAIICHI SANKYO	1	0
94	Fentanyl Oral Citra		0.408	SANDOZ	patent expired	
95	Requip	1	0.407	SMITHKLINE BEECHAM	1	1
96	Boniva	2	0.404	ROCHE	1	0
97	Caduet	6	0.388	PFIZER	2	1
98	Avapro	2	0.384	SANOFI AVENTIS US	1	0
99	Gleevec	3	0.384	NOVARTIS	1	0
100	Kaletra	15	0.373	ABBOTT	1	0

101	Ortho Tri-Cyclen Lo	1	0.371	ORTHO MCNEIL JANSSEN	1	1
102	Benicar	2	0.369	DAIICHI SANKYO	1	0
103	AndroGel	1	0.366	UNIMED PHARMS	1	0
104	Xopenex	6	0.354	SEPRACOR	2	1
105	Procrit		0.353	ORHTHO BIOTECH INC	patent expired	
106	Lamisil Oral		0.339	NOVARTIS PHARMACEUTICALS	patent expired	
107	Avalide	2	0.328	SANOFI AVENTIS US	1	0
108	Nasacort AQ	2	0.318	SANOFI AVENTIS US	1	0
109	Combivir	4	0.318	GLAXOSMITHKLINE	1	0
110	Allegra-D 12 Hour	9	0.316	SANOFI AVENTIS US	3	3
111	Duragesic		0.306	ORTHO MCNEIL JANSSEN	patent expired	
112	Copaxone	7	0.303	TEVA	1	0
113	RenaGel	5	0.293	GENZYME	1	0
114	Femara	1	0.293	NOVARTIS PHARMS	1	0
115	Enbrel Sureclick		0.293	AMGENA AND WYETH PHARMA	patent expired	
116	NovoLog Mix 70/30	5	0.292	NOVO NORDISK INC	1	0
117	Clarinex	5	0.288	SCHERING	2	1
118	Aldara	2	0.287	GRACEWAY	1	1
119	Forteo	5	0.282	LILLY	1	0
120	Suboxone		0.282	RECKITT BENCKISER	patent expired	
121	Avodart	3	0.281	GLAXOSMITHKLINE	1	1
122	Paxil CR	8	0.28	GLAXOSMITHKLINE	2	2
123	Norvir	8	0.275	ABBOTT	1	0
124	Avandamet	6	0.275	PHARMCO	2	2
125	Restasis		0.274	ALLERGAN	patent expired	

126	Avonex		0.266	BIOEN IDEC INC.	patent expired	
127	Sensipar	4	0.266	AMGEN	2	2
128	Tarceva	3	0.263	OSI PHARMS	2	1
129	Patanol	2	0.258	ALCON	2	1
130	Yaz	10	0.254	BAYER HLTHCARE	2	1
131	Lovaza	3	0.252	SMITHKLINE BEECHAM	1	1
132	Mirapex	3	0.249	BOEHRINGER INGELHEIM	2	1
133	Focalin XR	7	0.249	NOVARTIS	2	2
134	Cosopt	3	0.242	MERCK	1	0
135	Zyvox	2	0.236	PHARMACIA AND UPJOHN	1	0
136	Epzicom	7	0.23	SMITHKLINE BEECHAM	3	2
137	NuvaRing	1	0.23	ORGANON USA INC	1	0
138	Actiq		0.23	CEPHALON	patent expired	
139	Fosamax Plus D	5	0.229	MERCK	1	0
140	Actoplus Met	5	0.229	TAKEDA GLOBAL	1	0
141	Lumigan	2	0.226	ALLERGAN	1	0
142	Rhinocort Aqua	3	0.225	ASTRAZENECA	1	0
143	Solodyn		0.224	MEDICIS	patent expired	
144	Thalomid	11	0.222	CELGENE	2	1
145	Fuzeon	3	0.22	ROCHE	2	2
146	Astelin	1	0.219	MEDA PHARMS	1	0
147	BenzaClin		0.213	SANOFI AVENTIS US	patent expired	
148	Relpax	2	0.212	PFIZER IRELAND	1	0
149	Viread	4	0.21	GILEAD	1	0
150	Casodex	1	0.207	ASTRAZENECA	1	0

151	Vigamox	3	0.207	ALCON	2	1
152	Vesicare	1	0.205	ASTELLAS	1	0
153	Humalog Mix 75/25 Pn	4	0.204	LILLY	1	0
154	Trizivir	7	0.203	GLAXOSMITHKLINE	2	1
155	Budeprion SR		0.201	TEVA PHARMACEUTICALS	patent expired	
156	Xeloda	2	0.201	HLR	2	1
157	Sustiva	7	0.2	BRISTOL MYERS SQUIBB	2	1
158	Levitra	1	0.197	BAYER HLTHCARE	1	0
159	Endocet		0.193	ENDO PHARMACEUTICALS	patent expired	
160	Risperdal Consta	16	0.193	ORTHO MCNEIL JANSSEN	2	1
161	Aggrenox	1	0.193	BOEHRINGER INGELHEIM	1	1
162	Humira Pen		0.191	ABBOTT PHARMACEUTICALS	patent expired	
163	Kadian	2	0.191	ALPHARMA PHARMS	1	0
164	Differin	2	0.188	GALDERMA LABS LP	1	0
165	Catapres-TTS		0.187	BOEHRINGER INGELHEIM	patent expired	
166	Alphagan P	5	0.186	ALLERGAN	1	0
167	Tussionex		0.179	UCB INC	patent expired	
168	Zyrtec Syrup	1	0.177	MCNEIL CONSUMER	1	1
169	Maxalt	3	0.176	MERCK	2	1
170	Zoloft	5	0.175	PFIZER	1	0
171	Prilosec	6	0.174	ASTRAZENECA	3	2
172	Ciprodex Otic	3	0.174	ALCON	2	1
173	Temodar	1	0.173	SCHERING	1	1
174	Tobradex		0.172	ALCON	patent expired	
175	Zyrtec-D	1	0.163	MCNEIL CONSUMER	1	1

176	Welchol	10	0.161	DAIICHI SANKYO	1	1
177	Maxalt MLT	3	0.161	MERCK	2	1
178	Asmanex	10	0.161	TWISTHALER SCHERING	1	0
179	Atacand	3	0.16	ASTRAZENECA	1	1
180	Coumadin Tabs		0.16	BRISTOL MYERS SQUIBB	patent expired	
181	Dovonex	3	0.159	LEO PHARM	1	0
182	Klor-Con		0.159	UPSHER SMITH	patent expired	
183	Pegasys		0.156	ROCHE	patent expired	
184	Ultram ER	1	0.155	BIOVAIL LABS INTL	1	1
185	Betaseron		0.151	BERLEX LABS	patent expired	
186	Zovirax Topical		0.151	GLAXOSMITHKLINE	patent expired	
187	Trinessa		0.151	WATSON PHARMACEUTICALS INC	patent expired	
188	Pulmozyme		0.15	GENENTECH	patent expired	
189	Neupogen		0.15	AMGEN	patent expired	
190	Humulin N		0.149	ELI LILLY & CO. INC	patent expired	
191	Micardis HCT	2	0.148	BOEHRINGER INGELHEIM	2	1
192	Ortho Evra	2	0.148	ORTHO MCNEIL JANSSEN	1	0
193	Allegra-D 24 Hour		0.148	SANOFI-AVENTIS PHARMACEUTICALS	patent expired	
194	Fentora	2	0.147	CEPHALON	1	1
195	Enablex	2	0.147	NOVARTIS	1	0
196	Famvir	5	0.146	NOVARTIS	1	0
197	Avinza	1	0.145	KING PHARMS	1	1
198	Prempro	1	0.144	WYETH PHARMS INC	1	0
199	Coreg CR	5	0.144	SB PHARMCO	3	2
200	Marinol	1	0.144	UNIMED	1	0