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Incrementalism in Pharmaceutical Research: Incentives and Policy Implications

Submitted for 3L Written Work Requirement and Course Paper for Food & Drug Law

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Abstract: The tremendous commercial success of drugs which scientific data suggest are of no benefit to most patients relative to pre-existing drugs is illustrative of a phenomenon in pharmaceutical markets whereby products can become commercially successful even though their social costs vastly outweigh their social benefits. This suggests that a confluence of market failures, patent laws and FDA regulation of pharmaceuticals is creating perverse incentives that both encourage inefficient allocation of resources and decrease consumer access. In this paper, I explore this phenomenon by addressing two related questions. First, how can incremental improvements in medications be characterized so as to identify which incremental research should be encouraged or discouraged by patent and regulatory law? And second, which doctrinal or policy levers should Congress and the courts use to reduce incentives for undesirable incrementalism? Part I of this paper describes the economic and legal context that must inform pharmaceutical policy. Part II attempts to characterize pharmaceutical innovations in terms of their social value and degree of innovation, and thereby to identify the types of innovations that patent law and FDA regulations should promote. Part III presents possible policy solutions for tailoring incentives to discourage undesirable forms of incrementalism and encourage valuable forms of innovation. In particular, mandatory and voluntary comparative testing of drugs, increasing the standard of nonobviousness for patentability, improvements to the patent application process, and penalties for holders of invalid patents in paragraph IV challenges are explored as means to enhance the correlation between the social benefits and royalties derived from pharmaceutical patents.

Incrementalism in Pharmaceutical Research: Incentives and Policy Implications

The practice of patent “evergreening” includes a variety of tactics whereby the holder of a patent right extends its legal rights to a product market beyond the statutory term of the patent. This practice is pervasive in the pharmaceutical industry. Some industry observers believe that evergreening strategies have the highest rate of return of any business activity that brand name manufacturers perform.¹ The most widely celebrated (and in other circles, denounced) evergreening strategy was executed by AstraZeneca PLC to protect the revenues of its best-selling gastroesophageal reflux (heartburn) medicine Prilosec. Prilosec was a break-through discovery in the treatment of heartburn and became one of the best-selling medicines in history. As the expiration of its seventeen-year patent term approached, AstraZeneca anticipated that it would face strong competition from generics, which would result in a substantial reduction in prices and billions less in annual revenues. In response to this threat, AstraZeneca developed a multi-pronged strategy, of which the most important initiative was the development of a “new and improved” heartburn drug called Nexium.

Nexium is a derivative of Prilosec: its active ingredient is one of the stereoisomers found in Prilosec. Although a purified stereoisomer can be more safe and/or effective than a mixture of stereoisomers, in the case of Nexium, it was neither. Nor was it expected to be. The *Wall Street Journal* reported that the AstraZeneca management team charged with responding to the Prilosec patent expiration believed that Nexium was among the poorest of the many drug solutions they had considered, and they did not expect it to be any better at curing heartburn than its predecessor.² They thought it might be a modest improvement in treating a less common indication, erosive esophagitis. The New Drug Application (“NDA”) they submitted

¹Gardiner Harris, *Bristol-Myers Lawyers Stymie Generic Rivals*, WALL STREET JOURNAL, Sep. 7, 2001, at C1.

²Gardiner Harris, *Drug Prices – Why They Keep Soaring — Fast Relief: As a Patent Expires, Drug Firm Lines Up Pricey Alternative — Prilosec’s Maker Is Switching Users to a Lookalike Pill While It Thwarts Generics — Mr. Young Scrapes to Afford It*, WALL STREET JOURNAL, Jun. 6, 2002, at A1.

to the Food and Drug Administration (“FDA”) for the approval of Nexium supported that assessment.³ AstraZeneca performed studies comparing 20mg of Prilosec to a *double* dose, 40mg, of Nexium. These studies showed similar or better results for Nexium. But no head-to-head trials at comparable doses showed better results for Nexium. The FDA medical examiner’s evaluation emphasized that the head-to-head trials of Nexium and Prilosec did not show that Nexium was superior to Prilosec.⁴ He described benefits of drug as “comparable to” Prilosec for treatment of erosive esophagitis and better than a *placebo* for treatment of gastroesophageal reflux disease.⁵

The medical community was unimpressed by the new drug. Thomas Scully, administrator of the Centers for Medicare and Medicaid Services told doctors they should be embarrassed if they prescribed Nexium, because it offered no marginal benefit relative to the older, cheaper drug.⁶ Kaiser-Permanente, the nation’s largest managed care organization, refused to make the switch from Prilosec to Nexium, arguing that “Nexium is clearly a no value-added drug.”⁷ Dr. Jerry Avorn, chief of Brigham and Women’s Hospital’s pharmacoepidemiology department wrote, “Nexium is not at all better in any meaningful way than Prilosec.”⁸

The prevailing medical opinion, however, was no barrier to the commercial success of Nexium. AstraZeneca spent hundreds of millions of dollars in a successful effort to move Prilosec users to Nexium. In order to extend the period during which to move patients to Nexium, AstraZeneca defended Prilosec’s market share by filing and defending a myriad of patents on Prilosec, such as patents on the drug’s coating and use in combination with antibiotics. Since the FDA approval process includes stays on the marketing of generic drugs while patent validity is litigated, even patents which were later found invalid could extend AstraZeneca’s

³FDA, Center for Drug Evaluation and Research, MEDICAL REVIEW, APPLICATION 21-153/21-154, Dec. 3, 1999.

⁴*Id.*, at 4-5, 6.

⁵*Id.*, at 2.

⁶Editorial, *Comparing Prescription Drugs*, NEW YORK TIMES, Aug. 27, 2003, at A20.

⁷Harris, *Drug Prices – Why They Keep Soaring*, *supra* note 2.

⁸Neil Swidey, *The Costly Case of the Purple Pill: The Story of One Blockbuster Heartburn Drug Tells You Everything You Need To Know About the High Cost of Prescription Medicine*, BOSTON GLOBE MAGAZINE, Nov. 17, 2002.

hold on the market. These delays generated millions of dollars in additional revenue from Prilosec and more time for the Nexium marketing campaign.⁹ More than a year after the expiration of the patent on Prilosec, despite the existence of a multi-billion dollar market, no generics had been launched. In fact, AstraZeneca's market share *increased* after the patent on Prilosec had expired.¹⁰ Class action suits alleging fraudulent marketing of Nexium as an improvement have been unsuccessful.¹¹ Today in the brand name drug industry, the Prilosec-Nexium story is touted as a tremendous success from which valuable lessons can be drawn.¹² Advising clients about how to retain market share through evergreening tactics has itself become a business.¹³

The pharmaceutical industry has defended its profits on the grounds that they are the well-deserved reward and necessary incentive for the development of valuable medications that improve health and save lives. As the Prilosec-Nexium story illustrates, however, under the current regulatory regime, drugs that provide few or no health benefits over their predecessors can generate great value for their patent owners. This situation reflects a serious market failure, resulting from the interaction of numerous imperfections in the market for pharmaceuticals, patent laws and FDA regulations. This should cause us to question whether the current regulatory structure for pharmaceutical research distorts incentives by overvaluing certain kinds of innovation.

This situation is made possible by the confluence of a number of market failures, including the existence of monopolies, informational asymmetries, and moral hazard. According to classical economic theory, an optimal allocation of resources is reached in the market for a good when it is priced such that the con-

⁹Harris, *Drug Prices – Why They Keep Soaring*, *supra* note 2.

¹⁰OBESEITY, FITNESS & WELLNESS WEEK, *Generic Drugs: Biogenerics Set to Command More Than 12B*, Feb. 5, 2005, at 719.

¹¹See DRUG INDUSTRY DAILY, *Federal Judge Dismisses Class-Action Lawsuit Challenging Nexium Marketing*, Nov. 11, 2005.

¹²See *e.g.*, *Generic Drugs: Biogenerics Set to Command More Than 12B*, *supra* note 10.

¹³For example, in 2004, as generic versions of the first biological drugs threatened the market share of brand name drugs, the pharmaceutical consulting firm Cutting Edge Information widely publicized and sold a report on leading manufacturers' strategies for fending off generic competition. Cutting Edge Information, *Combating Generics: Pharmaceutical Brand Defense*, available at <http://www.pharmagenerics.com> (last visited Jan. 27, 2006); DRUG WEEKLY, *Average Pharmaceutical Brand Saves \$40.3M with Lifecycle Management Tactics*, Nov. 4, 2005, at 431.

sumer's marginal utility is equal to the producer's marginal cost. Production is then at the socially optimal level, because production takes place while marginal benefit is greater than marginal cost, but no further.¹⁴ The market for pharmaceuticals, however, deviates from the classical market in a number of important ways. First, the patent law intentionally creates monopolies for inventions.¹⁵ Where a single producer has a monopoly on production of a good, the monopolist can produce less than the optimal amount and raise the price above its marginal cost. In this scenario, some production that would take place in a competitive market, for which the consumers' marginal utility exceeds marginal cost, will not take place. This results in inefficiently low production. In addition, although the classical economic model does not address ability to pay, the high prices are by themselves a substantial barrier for consumers.

The policy justification for the creation of monopolies by patent law is that this grant will encourage further progress in the field. The statutory requirements for obtaining a patent are meant to generally identify those inventions that represent such progress.¹⁶ In the pharmaceutical field, however, additional regulations governing FDA pre-marketing approval can make even a patent that is likely to be declared invalid for its failure to meet the statutory standards a useful tool for its owner, because generic entry is prohibited while patent validity is being litigated. In industries other than the pharmaceutical industry, a patent which is likely to be found invalid has limited value to its owners, since it cannot be used to obtain a preliminary injunction against potential competitors. In the pharmaceutical industry, by contrast, a low-quality patent can generate substantial revenues, and thus the industry has powerful incentives to file for such patents.

The classical economic model of competitive markets also assumes perfect information. In a world of perfect

¹⁴EDWARD M. GRAMLICH, A GUIDE TO COST-BENEFIT ANALYSIS, 12 (1990).

¹⁵This is not to say that the exclusive rights to a particular product guaranteed by a patent necessarily correspond to a product market, however. A pharmaceutical patent holder has a monopoly on a particular product or method, but the patented invention may have competition from other products that treat the same illness. An economic monopoly results, however, where there are no substitutes available for the patented invention.

¹⁶35 U.S.C. §§101, 271 (2006). The Constitution empowers Congress to grant patents. ("The Congress shall have power...to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." U.S. CONST., art I., §8, cl. 8.) Pursuant to its Art. I power, Congress has enacted a series of Patent Acts which define the property rights to be given to inventors. Under the Patent Act, in order for a patent to issue, the invention must be new, useful, and nonobvious. 35 U.S.C. §§101-103 (2006).

information, consumers would be willing to pay more for products that produce greater health benefits and less for products that produce lesser benefits. This is a particularly problematic assumption in healthcare markets in which consumers do not possess the expertise required to decipher the pharmacological data. Physicians are in a better position to make assessments of quality, but they are not required to study new drug products as a condition of licensure and a large proportion learn about new drugs primarily from drug manufacturers' marketing campaigns.¹⁷ Even for those physicians who make serious efforts to educate themselves, data about the comparative effects of drugs is often unavailable or insufficient (*see* "Mis-valued Innovation," Part III. A., *infra*). Moreover, even if physicians are well-informed, pressure from misinformed patients influenced by advertising may affect prescribing.¹⁸ Imperfect information thus weakens the correlation between the health benefits of a drug and its market success.

Finally, prescription drug markets are affected by the problem of "moral hazard" that is typical of markets in which third party payers (insurers) pay for a substantial amount of the cost of the product, rather than the consumer himself. Since insurance reduces the price of drug products to consumers, consumer demand increases such that consumers will buy products that have less marginal value to them than they cost to produce. Prescribing physicians also pay none of the price of the drug, so unless an insurer's utilization management plan affects their prescribing choices, they have no economic incentive to seek more cost-effective alternatives. This combination of consumer and physician inattention to price results in inefficiently high demand.¹⁹

The confluence of these three market failures created the imperfect market in which the Prilosec-Nexium strategy could be successful. A manufacturer had the first effective drug in its class for which a patent was granted and created a temporary economic monopoly. As this monopoly neared expiration, it took advan-

¹⁷JERRY AVORN, POWERFUL MEDICINES: THE BENEFITS, RISKS AND COSTS OF PRESCRIPTION DRUGS, 279-281 (2004).

¹⁸*See* Michael S. Wilkes, Robert A. Bell, and Richard L. Kravitz, *Direct-to-Consumer Prescription Drug Advertising: Trends, Impact and Implications*, HEALTH AFFAIRS, Mar./Apr. 120 (2000) (surveying literature suggesting that direct-to-consumer advertising may lead to inappropriate prescribing).

¹⁹CHARLES E. PHELPS, HEALTH ECONOMICS, 289 (1992).

tage of the FDA regulations governing the approval process to prevent the entry of generic drugs and moved patients to another patented drug. Consumers, who do not have the expertise to evaluate the difference between Nexium and Prilosec and were shielded from direct costs by their insurance plans, were influenced by Nexium marketing. Meanwhile, many physicians did not act as effective gatekeepers. As a result, the common assumption that a large number of people would not buy a more expensive drug unless it offered a real improvement over a cheaper drug (an assumption that would make sense in a truly competitive market) was proven wrong.

The success of Nexium is illustrative of a phenomenon in pharmaceutical markets whereby products can become commercially successful even though their social costs vastly outweigh their social benefits. It might be argued that although studies showed that Nexium offered no improvement on average over Prilosec, it probably was a significant benefit for a small, unknown population of patients. However, the runaway commercial success of the drug suggests that a much larger population of people were paying for the more expensive of two equally effective drugs. It seems likely then that Nexium represents a kind of innovation for which social costs outweigh social benefits. This then suggests that patent law and related FDA regulation of pharmaceuticals is creating perverse incentives that both encourage inefficient allocation of resources and decrease consumer access.

In this paper, I will explore this phenomenon by addressing two related questions. First, how can incremental improvements in medications be characterized in order to identify which incremental research projects should be encouraged or discouraged by patent and regulatory law? And second, which doctrinal or policy levers should Congress and the courts use to reduce incentives for undesirable incrementalism?

Part I of this paper describes the economic and legal context that must inform pharmaceutical policy. Part II attempts to characterize incrementalism; what categories of inventions should patent and FDA policy encourage? Part III will present possible policy solutions for tailoring incentives to discourage undesirable

forms of incrementalism. In particular, mandatory and voluntary comparative testing of drugs, increasing the standard of nonobviousness for patentability, improvements to the Patent and Trademark Office (“PTO”) process, and penalties for using patents ultimately found invalid by the courts to delay generic competition will be explored as means to enhance the correlation between the social benefits and royalties derived from pharmaceutical patents.

I. CONTEXT AND MOTIVATION

In order to set the stage for a discussion of the intersection of policy and pharmaceutical innovation, this section discusses 1) the healthcare spending “crisis” as it relates to pharmaceuticals, 2) the particular importance of patents to the pharmaceutical industry, and 3) the regulatory framework for pharmaceutical research and industry responses to it.

I. A. The Healthcare Crisis and Access to Pharmaceuticals

Pharmaceutical industry profits have attracted intense scrutiny due largely to concerns that rising prices have made pharmaceuticals unaffordable for the middle class. Drug costs accounted for 12.4% of healthcare spending in 2001 and prescription drugs are one of the fastest growing categories of that spending.²⁰ From 1997 to 2001, spending on prescription drugs increased by an average of 14.5% annually, and studies predict growth rates between 8 and 11% through 2012, reflecting increases in both price and utilization.²¹ Industry

²⁰David Wessel, *The Economy; Capital: The Misconceptions About Drug Prices*, WALL STREET JOURNAL, May 6, 2004, at A2.

²¹Bradley C. Strunk, Paul B. Ginsburg, and Jon R. Gabel, *Tracking Health Care Costs: Growth Accelerates Again in 2001*, HEALTH AFFAIRS- WEB EXCLUSIVE, Sept. 25, 2002, available at

supporters argue that the primary reason for the increase in total drug costs is the availability of more effective drugs.²² Whether this claim is true or not, it is clear that increasing prices are putting the benefits of drug therapies out of the reach of a growing number of consumers, and putting increasing pressure on the budgets of state governments.

Privately-insured individuals are under increasing pressure from rising drug costs, as health insurance premiums are increasing faster than general price increases and growth in the economy.²³ A study published in 2000 reported that prescription drug prices had increased by 18.4% that year, accounting for 44% of the increase in health costs covered by private insurance.²⁴ As prescription drug prices have increased, health insurers have responded by limiting coverage and increasing coinsurance, leaving individuals with mounting exposure to rising drug prices.²⁵ As a result, although prescription drugs account for only about 12% of healthcare expenditures, they account for nearly a quarter of out-of-pocket costs for individuals.²⁶

Many Americans, whether insured or uninsured, are unable to afford the drugs prescribed for them. In 2000, roughly 53 million non-Medicare recipients lacked insurance coverage for prescription drugs.²⁷ A 1998 study reported that 42% of uninsured Americans and 17% of all Americans reported not filling prescriptions for

<http://content.healthaffairs.org/cgi/content/full/hlthaff.w2.299v1/DC1> (last visited Apr. 21, 2006); Stephen Heffler, Sheila Smith, Sean Keehan, M. Kent Clemens, Greg Won, and Mark Zezza, *Health Care Spending Projections for 2002-2012*, HEALTH AFFAIRS -WEB EXCLUSIVE, Feb. 7, 2003, available at <http://content.healthaffairs.org/cgi/content/full/hlthaff.w3.54v1/DC1?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&author1=heffler> (last visited Apr. 20, 2006); Christine Borger, Sheila Smith, Christopher Truffer, Sean Keehan, Andrea Sisko, John Poisal, and M. Kent Clemens, *Health Spending Projections Through 2015: Changes On The Horizon*, HEALTH AFFAIRS- WEB EXCLUSIVE, Feb. 22, 2006, at W70.

²² See e.g., Doug Bandow, *Demonizing Drugmakers: The Political Assault on the Pharmaceutical Industry*, POLICY ANALYSIS, May 8, 2003, at 1.

²³ Jon R. Gabel, Gary Claxton, Isadora Gil, Jeremy Pickering, Heidi Whitmore, Benjamin Finder, Samantha Hawkins, and Diane Rowland, *Health Benefits in 2005: Premium Increases Slow Down, Coverage Continues to Erode*, HEALTH AFFAIRS, Sep./Oct. 2005, at 1280.

²⁴ Christopher Hogan, Paul B. Ginsburg, and Jon R. Gabel, *Tracking Healthcare Costs: Inflation Returns*, HEALTH AFFAIRS, Mar./Apr. 2001 at 193-203.

²⁵ More than 40% of large employers say they are “very likely” to increase employee contributions to healthcare coverage in 2006. Gabel, *Health Benefits in 2005*, *supra* note 23, at 1279-80; see also Borger, *Health Spending Projections Through 2015*, *supra* note 21.

²⁶ Leila Abboud, *Stung By Distrust, Drug Makers Seek to Heal Image*, WALL STREET JOURNAL, Aug. 26, 2005 at B1.

²⁷ U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, PRESCRIPTION DRUG COVERAGE, SPENDING UTILIZATION AND PRICES, REPORT TO THE PRESIDENT, April 2000 (quoted in Public Citizen’s Congress Watch, *America’s Other Drug Problem: A Briefing Book on the Rx Drug Debate*, 2003, available at www.citizen.org/rxfacts).

financial reasons.²⁸ Similarly, a 2003 survey revealed that 13% of all adults (including the insured) and 11% of Medicaid enrollees did not obtain prescribed drugs due to out-of-pocket costs.²⁹

Proponents of high coinsurance plans (or “consumer-driven healthcare”) argue that increasing coinsurance is a necessary response to the problem of moral hazard. The insured, they contend, now consume healthcare services with little regard for cost. But if required to pay for some share of the cost, they will seek out low-cost, high-quality healthcare goods and services.³⁰ However, studies of prescription drug consumption belie this logic. They show that cost-saving strategies which shift expenses to patients have deleterious effects on access to prescription drugs across a wide range of therapeutic categories, including those considered “essential.”³¹ Having multiple chronic conditions strongly increases the probability of having prescription drug access problems.³² In other words, increasing patient exposure to prices discourages not just utilization that could be described as unnecessary or inefficient, but also utilization that is medically necessary, but beyond the means of patients.

Increasing costs for pharmaceuticals are also putting tremendous pressure on state budgets. Medicaid out-patient drug spending increased 18% annually between 1999 and 2002, compared to 10% for all health services.³³ As a share of total Medicaid spending, drug spending doubled in the 1990s from 5.6% of total spending in 1992 to 12% in 2002.³⁴ This phenomenon has focused legislative attention on the pharmaceutical industry at both the national and state levels. To contain increasing costs, almost all states have implemented strategies to curtail use.³⁵ In some cases, state officials have openly defied federal law in their efforts

²⁸Karen Donelan, Robert J. Blendon, Cathy Schoen, Karen Davis, and Katherine Binns, *The Cost of Health Care System Change: Public Discontent in Five Nations*, HEALTH AFFAIRS, May/June 1999, at 214.

²⁹Peter J. Cunningham, *Medicaid Cost Containment and Access to Prescription Drugs*, HEALTH AFFAIRS, May/June 2005, at 784.

³⁰See e.g., Regina Herzlinger, *Consumer-Driven Health Care: Containing the Health Care Cost Monster*, JOURNAL OF FINANCIAL SERVICE PROFESSIONALS, Mar. 2004, available at http://www.manhattan-institute.org/html/_jfsp-consumer.htm.

³¹Cunningham, *Medicaid Cost Containment and Access to Prescription Drugs*, *supra* note 29, at 788.

³²*Id.*, at 785-86.

³³*Id.*

³⁴*Id.*

³⁵*Id.*, at 780; also see Borger, *Health Spending Projections Through 2015*, *supra* note 21, at W67.

to address the growth of problem.³⁶

Advocates for the pharmaceutical industry argue that private charity should be used to make pharmaceuticals more available to the needy.³⁷ This argument, however, overlooks the fact that the prices of many drugs have sky-rocketed beyond the means of the middle class, meaning that the class of people potentially in need of charitable assistance is much larger than the indigent. For example, the cost of commonly used cancer drug therapies can cost tens or hundreds of thousands of dollars (*see* Table 1, *infra*) and even insured patients often accrue thousands of dollars in copayments for these drugs.³⁸

Table 1: Sample of 2005 Drug Prices

	Major Indication	Price of Year's Supply	
Gleevac	Cancer	\$37,000	
Avastin ³⁹	Cancer	\$100,000	
Erbitux	Cancer	\$120,000	
Fabrazyme	Fabry Disease	\$175,000-\$200,000	

Drug manufacturers have responded to the growing crisis in affordability, not by reducing prices, but by devising strategies to sustain the current level of pricing, while forgoing consumers their share of the price. Most commonly, drug manufacturers donate money to charities that help patients pay for their share of drug costs or their health insurance premiums.⁴⁰ This allows drug manufacturers to charge prices that would make their drugs otherwise unaffordable even to insured patients. By helping patients cover copays and premiums, the manufacturer ensures that the patient will be able to continue taking the medication, so

³⁶See *e.g.*, Letter to Governor Pawlenty, Minnesota, from William Hubbard, FDA, May 24, 2004, at http://www.fda.gov/imported_drugs/pawlenty0524.html (last visited June 8, 2004) (arguing that the creation of Minnesota RxConnect website, which facilitates the purchase of prescription drugs re-imported from Canada, violates federal law).

³⁷Bandow, *Demonizing Drugmakers*, *supra* note 22, at 36-37.

³⁸Geeta Anand, *Support System: Through Charities, Drug Makers Help People – and Themselves*, WALL STREET JOURNAL, Dec. 1, 2005, at A1.

³⁹Alex Berenson, *A Cancer Drug Shows Promise, at a Price That Many Can't Pay*, New York Times, Feb. 15, 2006, available at <http://www.nytimes.com/2006/02/15/business/15drug.html?ex=1145764800&en=e5b12b1ffbbbf84e&ei=5070#>. (The price for Avastin increased since the Anand article was published.)

⁴⁰See Anand, *Support System*, *supra* note 38.

the manufacturer can continue to bill the insurance company for its share of the expense. The insurance company then distributes the costs among its beneficiaries in the form of higher premiums. When soliciting contributions from drug manufacturers, these charities emphasize that the contributions lead to increased profits for manufacturers. For example, by donating \$5,400 to cover a premium for a patient who needs Fabrazyme, Genzyme can then charge the patient's insurer for the remainder of the \$175,000-\$200,000 annual price.⁴¹ Genzyme's net revenue from the transaction would be about \$185,000. Consumers, of course, eventually pay for the amount covered by insurance via their health insurance premiums. In addition, the drug manufacturer benefits from the opportunity to sell more product at nearly full price, and can take a tax deduction for its charitable contributions. Charities report that they expect their business to expand substantially when Medicare Part D becomes effective since beneficiaries will have to come up with thousands of dollars in copayments for covered drugs.⁴²

While pharmaceutical company funding of copays and premiums solves immediate affordability issues for some patients, the data on the failure of insured patients to obtain prescribed medications suggests that it is failing to reach a significant number of consumers. Furthermore, such programs contribute to the rising cost of health insurance coverage. Thus, there is continued pressure from consumer groups and insurers to address the issue of rising pharmaceutical prices.

⁴¹ *Id.*

⁴² *Id.*

I. B. Importance of Patent Protection to the Pharmaceutical Industry

I. B. 1. Patents and the Pattern of Innovation

Supporters of the pharmaceutical industry defend the high costs of prescription drugs on the grounds that these revenues are necessary incentives for further innovation. Strong patent protections are needed to ensure that pharmaceutical firms can charge enough to generate sufficient returns for investors. Controls on pricing or weakening of patent protection, they argue, would therefore slow the pace of innovation.⁴³

The contention that current high prices are needed to ensure continued innovation finds support in economic scholarship. Simulations by Giaccotto *et al.* suggest that research and development (“R&D”) spending would have been 30% lower if the federal government had limited the rate of growth of drug prices to the rate of growth of the CPI during the 1980s and 1990s. This would have resulted in one-third (or 330–365) fewer drugs being brought to market during that period.⁴⁴ Conversely, Giaccotto *et al.* found that R&D spending increases with real drug prices, and estimated that a 10% increase in drug prices is associated with a 6% increase in R&D intensity.⁴⁵ Thus, policy-makers seeking to directly control prices would have to weigh the social benefits of increased consumer access to needed pharmaceuticals against the social costs of slower innovation.⁴⁶

Pharmaceutical manufacturers also argue that strong patent protection, which underlies current pricing levels, is necessary for the flourishing of pharmaceutical research. Patents confer upon their owners the exclusive right to make, use and sell the patented invention for a twenty-year period from the date of

⁴³ See *e.g.*, Bruce N. Kuhlik, *The Assault on Pharmaceutical Intellectual Property*, 71 U. Chicago L. Rev. 93, 106-07 (2004). Mr. Kuhlik is the Senior Vice President and General Counsel of the Pharmaceutical Research and Manufacturers of America, the pharmaceutical industry’s lobbying organization.

⁴⁴ Carmelo Giaccotto, Rexford E. Santerre, and John A. Vernon, *Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry*, 48 Journal of Law and Economics 195, 195 (2005).

⁴⁵ *Id.*

⁴⁶ *Id.*, at 212.

application filing. Patents are thus an exception to the background rule of free market competition, since they provide their owners with a limited-term monopoly on their invention. This provides the inventor with an opportunity to be the exclusive supplier of his invention, and if the invention is commercially viable, to recoup his costs without competition from copycat competitors.

The common justification for patents is that they promote scientific progress. However, the twenty-year patent term is uniform across inventions. Despite the utilitarian rationale of patent law, Congress has not attempted to tailor the patent term to particular types of inventions so as to ensure that inventors face optimal incentives for invention that neither under-reward nor over-reward their contributions to society.⁴⁷ Thus, it would be mere coincidence if the current twenty-year term were an optimal reward for pharmaceutical inventions.

Patents, moreover, are not the only way to ensure that innovators can recoup their costs. The advantages of being first-to-market, marketing and service efforts, and the secrecy and complexity of product technology can give innovators a market advantage which allows them to recover their costs even in the absence of patent protection.⁴⁸ There is, however, both empirical and theoretical support for the proposition that the pharmaceutical industry is particularly reliant on patent protection. Surveys of R&D managers in a variety of industries have found that managers in the pharmaceutical industry placed the highest importance on patents as a means of recovering the costs of innovation.⁴⁹ In contrast, managers in other research-intensive industries placed greater importance on other factors, such as efficiencies in production and first-mover advantage.⁵⁰

⁴⁷See Edward C. Walterscheid, *Defining Patent and Copyright Term: Term Limits and the Intellectual Property Clause*, 7 J. INTELL. PROP. L. 315 (2000) (historical account of the origin of the patent term in 17th century British legal practice).

⁴⁸Henry Grabowski, *Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, in John Duca, ed., *SCIENCE AND CENTS: THE ECONOMICS OF BIOTECHNOLOGY*, Federal Reserve Bank of Dallas, 2003, at 3, available at <http://www.econ.duke.edu/Papers/Other/Grabowski/Patents.pdf>.

⁴⁹Richard C. Levin, *et al.*, *Appropriating Returns from Industrial Research and Development*, BROOKINGS PAPERS ON ECONOMIC ACTIVITY 783-820 (1987); Wes Cohen *et al.*, "Appropriability Conditions and Why Firms Patent and Why They Do Not in the American Manufacturing Sector," Working Paper (Carnegie-Mellon University 1997).

⁵⁰*Id.*

The argument that patents are particularly necessary to pharmaceutical research also finds support in the pattern of pharmaceutical innovation. Since the relationship between the structure and biochemical function of chemicals is so unpredictable, research is subject to an unusual degree of uncertainty and requires costly experimentation. Once a new chemical product is discovered, it is usually easy for competitors to determine how to copy it. The costs of imitation for competitors are so low relative to the initial cost of developing a new commercial product (*see* Part I. B. 2., *infra*) that in the absence of patent protection, the prices set in free markets would most likely be too low to cover the costs of development.⁵¹

I. B. 2. Cost of Innovation: Estimated R&D Expense per New Chemical Entity

1. B. 2. a. Cost Drivers

Support for the argument that pharmaceutical innovation is exceptionally expensive can be found in the academic literature. In a widely-publicized study, a team of researchers led by Joseph DiMasi at the Tufts Center for the Study of Drug Development published their finding that the average cost of research and development for a new chemical entity (including the costs of failed attempts) is 802 million dollars.⁵² DiMasi *et al.* collected data on R&D expenditures on a randomly selected sample of investigational drugs that were developed entirely in-house from 10 pharmaceutical firms, including both U.S. and foreign-owned companies.⁵³ The firms themselves provided the R&D cost data. The drugs in the study did not receive

⁵¹Grabowski, *Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, *supra* note 48, at 4.

⁵²Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECONOMICS 151-185 (2003); *But see* Arnold S. Relman and Marcia Angell, *America's Other Drug Problem*, THE NEW REPUBLIC, Dec. 16, 2002, at 28-30; and Public Citizen's Congress Watch, *America's Other Drug Problem: A Briefing Book on the Rx Drug Debate*, 2003, available at <http://www.citizen.org/documents/dbbapril.pdf>.

⁵³DiMasi, *The Price of Innovation: New Estimates of Drug Development Costs*, *supra* note 52, at 156.

federal funding at any stage of development, and in this sense are arguably atypical.⁵⁴ The cost estimate therefore may overstates the R&D investment that the manufacturer itself needs to make in an average case.⁵⁵

The pharmaceutical industry is the beneficiary of substantial publicly-funded research. In a 1995 study by MIT, the study authors found that publicly-funded research was a “critical contributor” to the discovery of nearly all of the 25 most important drugs introduced between 1970 and 1995.⁵⁶ Similarly, an National Science Foundation study found that 50% of scientific research cited in drug and medicine patents was funded by the federal government, while only 17% was funded by private industry.⁵⁷ Technology transfer statutes, including the Bayh-Dole Act of 1980 and the Federal Technology Transfer Act of 1986, permit private drug manufacturers to seek patent rights on federally-funded research.⁵⁸

In addition, it is important to note that the cost estimate applies only to new chemical entities, not all drug products. New formulations and delivery methods are not taken into account, although they account for about a third of R&D spending.⁵⁹ An average cost which did include these products would substantially drive down the cost estimate. It is important to note therefore, that DiMasi’s results do not reflect the cost of an average new drug, but only those new drugs that contain an active ingredient that has not been

⁵⁴Public Citizen’s Congress Watch, *America’s Other Drug Problem: A Briefing Book on the Rx Drug Debate*, *supra* note 52, at 48.

⁵⁵*But see* DiMasi, *The Price of Innovation: New Estimates of Drug Development Costs*, *supra* note 52, at 56-57.

⁵⁶Artie K. Rai, *Symposium: Intellectual Property Challenges in the Next Century: The Information Revolution Reaches Pharmaceuticals: Balancing Innovation Incentives, Cost and Access in the Post-Genomics Era*, 2001 U. ILL. L. REV. 173, 185 fn. 53 (2001).

⁵⁷*Id.*, at 185 fn. 54.

⁵⁸*Id.*, at 185-86 fn. 56. The Bayh Dole Act was enacted to promote the commercialization of scientific discoveries made with federal funding. 35 U.S.C. §200 (2006). It did so by authorizing private parties who engaged in federally-funded research to retain title to their inventions, subject to reservation of a royalty-free nonexclusive license to the federal government. 35 U.S.C. §202 (2006). *See generally*, Rebecca S. Eisenberg, *Symposium on Regulating Medical Innovation: Public Research and Private Development: Patent and Technology Transfer in Government-Sponsored Research*, 82 Va. L. Rev. 1663, 1665 (1996). The Federal Technology Transfer Act authorized government laboratories to enter joint development agreements with industry and to agree to assign patents on inventions made by federal employees to the private firm or its employees, subject to reservation of a royalty-free license. 15 U.S.C. §3710 (2006). *See generally, id.* at 1706-1707.

⁵⁹*Pharmaceutical Investment and Output*, PROCEEDINGS OF THE CMR INTERNATIONAL, 2002 (quoted in Richard G. Frank, Editorial, *New Estimates of Drug Development Costs*, 22 J. HEALTH ECONOMICS, 325, 327 (2003)).

approved for use in some other form.

The average cost calculated by DiMasi *et al.* does take into account the costs of the large proportion of R&D efforts that are unsuccessful by aggregating these costs with the costs of successful projects.⁶⁰ Most drug candidates which are initially investigated for use in humans will fail to reach market: less than 1% of compounds in pre-clinical trials advance to clinical trials. Only about 20% of these gain FDA approval.⁶¹ Stated differently, of every 100 drugs for which investigational new applications are submitted to the FDA, 70 will successfully complete Phase 1 human trials. Thirty-three will complete Phase 2, 25 to 30 will complete Phase III and 20 will be ultimately approved for sale.⁶² Thus, the revenues for successful drugs must be sufficient to provide an incentive to pursue research that has a very high failure rate.

Although the \$802 million figure is often cited as the “average cost of research and development,” the authors of the study are careful to note that only about half of this figure, \$403 million, represents the out-of-pocket costs that the drug developer actually incurs. Clinical trial costs account for the largest portion of out-of-pocket expenses.⁶³ The other \$399 million is the opportunity cost of investing in R&D rather than investing in another activity with an 11% rate of return.⁶⁴

Industry critics have challenged this cost estimate, arguing that the true cost of new chemical entity may be as low as \$100 million.⁶⁵ They point out that the data relied upon by the DiMasi study is provided by the pharmaceutical industry itself, which has a strong interest in justifying its pricing decisions, and no data is publicly available to verify it.⁶⁶ Thus, it is impossible to tell what expenses have been categorized by the industry as “development” that are more appropriately categorized as marketing.⁶⁷

⁶⁰DiMasi, *The Price of Innovation: New Estimates of Drug Development Costs*, *supra* note 52, at 152-53.

⁶¹Joseph A. DiMasi, *Success Rates for New Drugs Entering Clinical Testing in the United States*, 58 *CLINICAL PHARMACOLOGY AND THERAPEUTICS* 1-14 (1995).

⁶²Michael S. Rosenwald, *A Small Drug Firm's Disappointment: After Failed Antibiotic Test, Advancis Aims to Regroup*, *WASHINGTON POST*, Jun. 17, 2005, at D1.

⁶³DiMasi, *The Price of Innovation: New Estimates of Drug Development Costs*, *supra* note 52, at 165.

⁶⁴*Id.*, at 63.

⁶⁵Relman, *America's Other Drug Problem*, *supra* note 52, at 30.

⁶⁶*Id.*, at 29.

⁶⁷*Id.*

A subsequent study by Bain Consulting, based on 2000-2002 R&D spending data, estimated that the average investment required to get a single drug to market has increased to \$1.7 billion.⁶⁸ Based on this number, Bain contends that only one out of six new drug prospects will deliver returns above the industry's risk-adjusted cost of capital.⁶⁹ The Bain press release does not mention for whom this study was commissioned but reads as if designed to market Bain's management consulting services to the pharmaceutical industry. Thus, it seems possible that the study was designed to present the highest plausible estimate. This number is not directly comparable to the DiMasi study, since it uses a substantially different methodology, but academic scholarship nonetheless supports the contention that the average cost of drug development is rising.⁷⁰

While the DiMasi and Bain estimates are likely both inflated by marketing expenses, there is no doubt that pharmaceutical research is both risky and extremely expensive. In addition, some historical data suggests that investment will flow elsewhere if prices decline substantially.⁷¹ These studies thus support the contention that for at least some subset of drugs, and particularly for new chemical entities, the current patent and regulatory protections are necessary to support continued innovation. They do not address, however, whether these protections are also necessary for other subsets of drugs.

⁶⁸Peter Landers, *Cost of Developing a New Drug Increases to About \$1.7 Billion*, WALL STREET JOURNAL, Dec. 8, 2003.

⁶⁹*Has the Pharmaceutical Blockbuster Model Gone Bust?*, BAIN AND COMPANY PRESS RELEASE, Dec. 8, 2003.

⁷⁰Henry G. Grabowski, *Are the Economics of Pharmaceutical Research and Development Changing? Productivity, Patents and Political Pressures*, 22 PHARMACOECONOMICS Suppl. 2: 15, 16 (2004). Among other things, the Bain study includes more marketing expenses, such as commercialization costs, like preparing marketing materials. Landers, *Cost of Developing a New Drug Increases to About \$1.7 Billion*, *supra* note 68.

⁷¹In the wake of the President Clinton's healthcare proposal, in which price controls were considered, investment in pharmaceutical research declined temporarily. Alan F. Holmer, *Pharmaceutical Research and Manufacturers of America, Letter, The Pharmaceutical Industry – To Whom Is It Accountable*, 343 NEW ENGLAND J. MED. 1415 (2000).

I. B. 2. b. How Much of Pharmaceutical Spending Is Marketing or Profit?

Subsidization of the private pharmaceutical industry through the patent and regulatory systems is justified by the importance of promoting the advance and application of biomedical science. However, industry critics argue that much of the activity that is subsidized is actually marketing and that the high profit margins of the industry suggest that current levels of subsidization are unnecessary. While there is strong public support for biomedical research, public subsidization of marketing expenses should be far more controversial, and there is evidence that a substantial amount of pharmaceutical company spending is directed toward marketing. The magnitude of marketing efforts is substantial even relative to impressive R&D spending. Public Citizen contends that Fortune 500 pharmaceutical firms spend more than three times as much on marketing as they do on R&D.⁷² Likewise, the *Wall Street Journal* estimated that pharmaceutical companies as a whole spend twice as much on marketing as they do on R&D.⁷³ Industry observers contend that the largest firms have shifted the core of their business away from the unpredictable task of creating drugs and toward the less risky business of marketing them.⁷⁴ AstraZeneca, for example, spent \$478 million in 2001 to persuade consumers to move from Prilosec, which was coming off patent, to the nearly identical patented drug, Nexium.⁷⁵ Industry critic Marcia Angell notes, “the less important a new drug, the more marketing is required to sell it.”⁷⁶

Critics of the pharmaceutical industry also contend that consistently high profit margins in the pharmaceutical industry belie claims that the prices currently charged for drugs are necessary for the survival of the

⁷²Public Citizen’s Congress Watch, *America’s Other Drug Problem: A Briefing Book on the Rx Drug Debate*, 2003, *supra* note 52, at 28.

⁷³Gardiner Harris, *New Script: Drug Firms, Stymied in the Lab, Become Marketing Machines*, WALL STREET JOURNAL, Jul. 6, 2000, at A1.

⁷⁴*Id.*

⁷⁵See Harris, *Drug Prices – Why They Keep Soaring*, *supra* note 2.

⁷⁶Marcia Angell, Letter, *The Pharmaceutical Industry – To Whom Is It Accountable*, 343 NEW ENGLAND J. MED. 1417 (2000).

industry and continued innovation.⁷⁷ In the last several years, the pharmaceutical industry has consistently ranked among the most profitable industrial sectors by three measures of profitability (*see* Table 2, *infra*).⁷⁸ Arguably, measures of profitability in research-based industries are complex enough to make cross-industry comparisons misleading;⁷⁹ and the pharmaceutical industry is the most research-intensive of U.S. industries that support their R&D with private funds.⁸⁰ Nonetheless, there is little doubt that the industry as a whole earns a handsome return on its investment relative to other major industries despite a worrying downward trend in the last few years.

Table 2: Pharmaceutical Industry Profits

	2002	2003	2004
Return on Revenues (Profits as % of revenue)	17.0% In- dus- try Rank: #1 of 48	14.3% In- dus- try Rank:# 3 of 47	15.5% In- dus- try Rank: #3 of 47
Return on Assets (Profits as % of assets)	14.1% Industry Rank: #1 of 48	10.3% Industry Rank:# 2 of 27	8.1% Industry Rank:# 12 of 47

⁷⁷Henry Grabowski, John Vernon, and Joseph A. DiMasi, *Returns on Research and Development for 1990s New Drug Introductions*, 20 PHARMACOECONOMICS Suppl. 3 11, 20 (2002).

⁷⁸*Fortune* reports three measures of profitability. Return on revenues (a.k.a. “profit margin”) calculates net income as a percent of revenues and gives the profit per dollar of sales. A high profit margin indicates that a company has flexibility to reduce its prices or absorb additional expense while remaining profitable. Return on assets is the ratio of net income to total assets. This indicates how much profit is generated by each dollar of assets. Since assets are usually reported at historical cost rather than fair market value, the total assets amount is usually very conservative and the ratio is artificially inflated. Return on equity is equal net income as a percent of total equity. This ratio provides a measure of how much return stockholders received from their investments. Since equity is difference between a company’s assets and its debt, return on equity measures how effectively management is using the owners’ investments to generate income. *See* Jeffrey H. Haas, CORPORATE FINANCE IN A NUTSHELL, 42-43 (2004).

⁷⁹Uwe Reinhardt, *Perspectives on the Pharmaceutical Industry*, HEALTH AFFAIRS, Sep./Oct. 2001, at 142-43.

⁸⁰F. M. Scherer, *The Pharmaceutical Industry – Prices and Progress*, 351 NEW ENGLAND JOURNAL OF MEDICINE, Aug. 26, 2004, 927, 927 (2004).

Return on Equity (Profits as % of equity)	27.6% Industry Rank: #2 of 48	22.1% Industry Rank: #4 of 27	16.6% Industry Rank: #13 of 47
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Source: Fortune 500⁸¹

The industry, however, is heavily reliant on so-called blockbuster drugs. Studies by Grabowski *et al.* show that the top 10% of drugs accounted for close to half of the overall market value associated with all new drug introductions.⁸² Only the top 10% of new chemical entities (“NCEs”) have returns that far exceed the average R&D cost (\$802 million) within the 7½ year period of market exclusivity afforded by the Hatch-Waxman provisions (see Part I.C., *infra* for discussion of the Hatch-Waxman Act).⁸³ Only 34% of NCEs have returns in excess of the average R&D outlay. Accordingly, the top 10% of NCEs account for approximately half of all revenues from new drugs. Although a drug whose revenues exceed variable costs (but not total costs) can contribute positively to a firm’s bottom line, in the long run, a firm must have a number of products whose returns significantly exceed total R&D costs in order to have a viable R&D program.⁸⁴ This suggests that reforms to the regulatory structure which reduce returns to NCEs, absent other corrective measures, would significantly reduce incentives to produce them and diminish the profitability of the industry as a whole.

⁸¹ *Fortune 500*, FORTUNE, Apr. 18, 2005, at F-26, F-28; *Fortune 500*, FORTUNE, Apr. 5, 2004, at F-26, F-28.

⁸² Grabowski, *Returns on Research and Development for 1990s New Drug Introductions*, *supra* note 77, at 11.

⁸³ Grabowski, *Are the Economics of Pharmaceutical Research and Development Changing?*, *supra* note 70, at 21. (7½ year period assumes that the brand name manufacturer will take advantage of the 30 month stay on generic approval.)

⁸⁴ Grabowski, *Returns on Research and Development for 1990s New Drug Introductions*, *supra* note 77, at 23.

I. C. The Regulatory Framework

In addition to patent protection, the pharmaceutical industry is the beneficiary of federal regulations whose effect is to subsidize pharmaceutical innovation, and in particular, to enhance the profitability of the blockbuster drugs. These regulations protect innovators against competition even after the original patent term expires. They include the market exclusivity and patent term restoration provisions of the Hatch-Waxman Act (discussed below), the Orphan Drug Act, and patent term extension for pediatric testing.

Drug manufacturers usually apply for a patent on a new drug after initial studies show that it may have beneficial biological activity, but before they complete the testing required for FDA approval.⁸⁵ The average remaining patent life for a drug after it obtains FDA approval is 11-12 years.⁸⁶ Thus, the manufacturer typically has 11-12 years to recover his investment, not the entire twenty-year term of the patent. The R&D phase and the first couple of years of marketing expenditures typically generate a stream of negative cash flows. Cash flows then become positive for the rest of the patent term, and decline rapidly upon patent expiration and the start of generic competition.⁸⁷

In 1984, Congress reacted to growing concern that patent terms were not long enough to ensure cost recovery by passing the Drug Price Competition and Patent Term Restoration Act, commonly known as “Hatch-Waxman.” The Hatch-Waxman Act has importantly shaped the nature of competition in the pharmaceutical industry. Its provisions reflect the twin goals of encouraging innovation by ensuring market exclusivity for sellers of newly-approved drugs, and encouraging generic competition for brand name drugs whose patents and marketing exclusivity terms have expired.

Hatch-Waxman contains several provisions intended to increase generic competition for drugs that come

⁸⁵Kuhlik, *supra* note 43, at 96-97.

⁸⁶Joseph A. DiMasi and Cherie Paquette, *The Economics of Follow-On Drug Research and Development*, 22 PHARMACOECONOMICS 1, 4 (2004).

⁸⁷Grabowski, *Returns on Research and Development for 1990s New Drug Introductions*, *supra* note 77, at 20.

off patent. First, it accelerates generic entry by allowing a streamlined approval process for generic drugs. Under the Food, Drug and Cosmetic Act (“FDCA”), a drug may not be marketed until the FDA approves its New Drug Application (“NDA”).⁸⁸ In order to obtain such approval, the applicant must submit data from animal and human studies that demonstrate its safety and efficacy. Prior to Hatch-Waxman, the innovating manufacturer and manufacturer of a generic copy were subject to the same testing requirements for FDA approval, and a generic manufacturer could not test its product during the patent term of the brand name drug without infringing the patent.⁸⁹ As a result, the generic manufacturer would have wait until the end of the patent term of the branded drug and independently prove the safety and effectiveness of its product. Hatch-Waxman eliminated this unnecessary (and arguably unethical) clinical testing by establishing the Abbreviated New Drug Application (“ANDA”) process for generic drug entry. Using the ANDA process, generics manufacturers may rely on the data submitted with the NDA for the branded drug and need only show bioequivalence to the branded product with the same active ingredient. Hatch-Waxman also creates a safe harbor from infringement to allow generic companies to perform activities necessary to develop a generic product, such as bioequivalence studies, during the term of the patent for the branded drug.⁹⁰ Although the testing required for an ANDA is significantly less expensive than that required for an New Drug Application (“NDA”), potential profitability is also much lower due to competition from the original manufacturer and other generic manufacturers.

As part of the ANDA, the generic manufacturer must certify whether the generic drug would infringe any patents. A generic manufacturer can certify that there are no relevant patents, that the relevant patents have expired, that the generic will not be marketed until after the relevant patent expires, or that the relevant patent is invalid or not infringed by the generic (“paragraph IV certification”). Patents that can serve as the basis for certification are found in the FDA’s list of “Approved Drug Products with Therapeutic

⁸⁸21 U.S.C. §355(a) (2006).

⁸⁹*Roche Products Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 863 (Fed. Cir. 1984).

⁹⁰35 U.S.C. §271(e)(1)-(2) (2006).

Equivalence,” a.k.a. “The Orange Book.”⁹¹ The FDA does not police what is listed in the Orange Book on the grounds that it is not competent to judge the validity of patents.⁹² Hatch-Waxman provides an incentive to challenge existing patents by granting a 180-day period of marketing exclusivity to the first generic manufacturer to challenge a patent and prevail.⁹³ The 180-day period starts on the date of the court’s determination that the patent is invalid or not infringed, or the marketing of the generic drug, whichever comes first. During the marketing exclusivity period, no other generic manufacturer may enter the market, which allows the first generic entrant to charge higher prices and establish a brand identity. The benefit of being first-to-market has created a powerful incentive for generics to challenge patent validity in court, and thus has led to extensive litigation.

These provisions of Hatch-Waxman substantially increased generic competition for off-patent drugs. Since its enactment, generics’ market share has increased from 19% to 48%.⁹⁴ Sales erosion for a product coming off patent now often occurs in a matter of months.⁹⁵ This increased availability of generics has had a significant impact on cost: a 1998 Congressional Budget Office (“CBO”) study showed that drugs which are available in both generic and brand-name versions are approximately half of the average price of a brand-name prescription. The CBO estimated that in 1994 alone the availability of generic drugs saved purchasers an estimated \$8 -10 billion.⁹⁶

The Hatch-Waxman Act also has provisions intended to ensure that the inventors of new drugs can recoup their R&D costs. First, it restores some of the patent term that is spent complying with FDA pre-marketing

⁹¹21 U.S.C. §355(b)(1) (2006).

⁹²FEDERAL TRADE COMMISSION, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY, Chapter 3, at 13 (2003).

⁹³21 USC §355(j)(5)(B)(iv) (2006).

⁹⁴Chris Adams and Gardiner Harris, *Drug Makers Face Battle to Preserve Patent Extensions — Governors Join Businesses, Labor Unions in Effort to Hasten Generics to Market*, WALL STREET JOURNAL, Mar. 19, 2002, at A24.

⁹⁵Grabowski, *Are the Economics of Pharmaceutical Research and Development Changing?*, *supra* note 70, at 19.

⁹⁶FEDERAL TRADE COMMISSION, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION, 9 (2002) (citing Congressional Budget Office, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY (July 1998) at 28, available at <<http://www.cbo.gov/showdoc.cfm?index'655&sequence'0>>).

approval requirements. Patent term extensions give back one-half of the time spent in clinical trials plus the time spent in the NDA approval process (between filing and approval) up to a maximum of five years (or fourteen years from the date of FDA approval).

Second, Hatch-Waxman grants limited periods of market exclusivity. The exclusivity provision operates by barring generic manufacturers from relying on the brand name company's safety and effectiveness data in the ANDA process. Five years of exclusivity are granted to each newly approved NCE regardless of patent status. Three years are granted to modifications of a drug whose active ingredient has already been approved by the FDA. (The value of the three-year marketing exclusivity period is limited, however, because doctors can prescribe drugs off-label and a generic will not infringe a method-of-use patent as long as it does not market the drug for the secondary indication for which exclusivity was granted.) An additional six months of exclusivity is granted for pediatric testing.⁹⁷

Furthermore, when a generic manufacturer undertakes a paragraph IV challenge to a patent, an automatic 30-month (two and a half year) stay on generic approval is triggered. This stay on generic approval is triggered regardless of the likelihood that the generic manufacturer will win on the merits of the suit. As a result, there is a 5-7½ year floor on market exclusivity for an NCE after FDA approval.⁹⁸ Under the original legislation, a brand-name firm could generate multiple 30-month stays by listing multiple patents late in the product's life cycle. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 limited each branded product to a single 30-month stay.⁹⁹ Even without the availability of additional 30-month

⁹⁷21 U.S.C. §355(a) (2006).

⁹⁸Grabowski, *Are the Economics of Pharmaceutical Research and Development Changing?*, *supra* note 70, at 20-21.

⁹⁹Pub. Law. 108-173, 117 Stat 2066, Dec. 8, 2003, Title XI—Access to Affordable Pharmaceuticals (HR 1). This Amendment to the bill was titled the "Greater Access to Affordable Pharmaceuticals Act." introduced in the Senate as S. 1225. June 10, 2003. See H. Res. 299 [Report No. 108-181]. Elimination of possibility of multiple 30 month stays: Medicare Act § 1101(2)(A), codified at 21 U.S.C. § 355(j)(5)(B)(iii).

stays, however, patents obtained after expiration of the original patent can still serve as the basis for an ordinary patent infringement suit.¹⁰⁰ Additional amendments to Hatch-Waxman restrict the availability of a 30-month stay to patents listed with the FDA before the generic application was filed and allow generic companies to seek patent delisting from the Orange Book as a counterclaim in an infringement suit.¹⁰¹

I.D. Anti-Generic Strategies

I.D. 1. Non-Patent Based

The legal framework created by Hatch-Waxman and other regulatory provisions has created opportunities for brand-name drug makers to develop strategies for keeping generics off the market.¹⁰² One strategy is to develop a modified formulation, such as a drug containing the same active ingredient as a blockbuster drug, which must be taken once a week instead of once a day. The modified version results in a three-year period of marketing exclusivity under the Hatch-Waxman provisions. In many states, the change prevents pharmacists from automatically substituting a generic for the reformulation of the brand-name drug, since the generic and the reformulated brand name drug are not exactly equivalent.¹⁰³ For example, in Massachusetts, state law requires pharmacists to substitute a generic drug (if available) for a brand name drug unless a physician writes “no substitution.”¹⁰⁴ This policy is intended to promote affordable access to drug therapies. Like some states, Massachusetts defines acceptable substitutes for a name brand drug largely based

¹⁰⁰FEDERAL TRADE COMMISSION, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION, *supra* note 96, at iv.

¹⁰¹Kuhlik, *supra* note 43, at 101.

¹⁰²Adams, *Drug Makers Face Battle to Preserve Patent Extensions*, *supra* note 94.

¹⁰³Gardiner Harris and Chris Adams, *Delayed Reaction: Drug Manufacturers Step Up Legal Attacks That Slow Generics — That’s One Reason It Takes FDA Longer to Approve Knock-Offs Than Brands — The ‘Metabolite Defense’*, WALL STREET JOURNAL, Jul. 12, 2001, at A1.

¹⁰⁴DIVISION OF HEALTHCARE FINANCE AND POLICY, *Healthpoint: What’s Driving Prescription Drug Costs*, Apr. 1999, at 2, available at http://www.mass.gov/Eeohhs2/docs/dhcfp/pdf/hp_13.pdf.

on whether the FDA has designated the generic as a therapeutic equivalent of the prescribed drug.¹⁰⁵ The FDA, however, will not rate a generic as therapeutically equivalent to the original drug unless it has the same dosage form and is bioequivalent.¹⁰⁶ Thus, by developing multiple formulations of a drug, manufacturers can evade regulatory schemes meant to increase use of generics. This provides an incentive for manufacturers to aggressively promote switching patients to the new formulation of the drug before patent expiration on the original.¹⁰⁷ For example, to reduce generic competition for its blockbuster diabetes drug Glucophage, Bristol Myers launched new formulations, including a version of Glucophage that can be taken once a day instead of twice a day. Bristol-Myers used coupons to encourage patients to switch to the once-a-day version for which it still had exclusive marketing rights.¹⁰⁸ Most patients, of course, were unaware that they were exchanging a drug that would soon have generic competition for one that would not.

Brand-name manufacturers also stave off generic competition by filing citizen petitions that raise safety objections to ANDAs for generics.¹⁰⁹ FDA regulations permit any citizen to raise safety concerns about a drug the FDA is reviewing. Eighty percent of such objections are either rejected by the FDA or withdrawn by the petitioner.¹¹⁰ The effect of rejected petitions is to delay the entry of generics into the market. This is one reason that the FDA takes longer to approve applications for generics, which should in theory be simpler, than it takes to approve new drugs.¹¹¹ FDA records show that in 2000, the median time for reviewing a generic drug application was 18.2 months, whereas a new drug application took 11.2 months.¹¹² In 2001, Senators Charles Schumer (D-NY) and John McCain (R-AZ) introduced a bill to block such tactics. It would

¹⁰⁵105 C.M.R. 720.050 (2006).

¹⁰⁶44 FR 2932 (January, 12, 1979) (proposed rule) and 45 FR 72582 (October 31, 1980) (final rule) (cited in THE NATIONAL INSTITUTE FOR HEALTH CARE MANAGEMENT, RESEARCH AND EDUCATIONAL FOUNDATION, *Changing Patterns of Pharmaceutical Innovation*, May 2002, at 18 fn. 31).

¹⁰⁷THE NATIONAL INSTITUTE FOR HEALTH CARE MANAGEMENT, RESEARCH AND EDUCATIONAL FOUNDATION, *Changing Patterns of Pharmaceutical Innovation*, *supra* note 106, at 17-18.

¹⁰⁸Harris, *Bristol-Myers Lawyers Stymie Generics*, *supra* note 1.

¹⁰⁹21 C.F.R. §10.30 (2005).

¹¹⁰Harris, *Delayed Reaction: Drug Manufacturers Step Up Legal Attacks That Slow Generics*, *supra* note 103; Adams, *Drug Makers Face Battle to Preserve Patent Extensions*, *supra* note 94.

¹¹¹Harris, *Delayed Reaction: Drug Manufacturers Step Up Legal Attacks That Slow Generics*, *supra* note 103.

¹¹²*Id.*

have required citizen-petitioners to better substantiate their challenges, and to prove they were not raising questions for anticompetitive reasons. The bill, however, failed to reach a committee vote.¹¹³

Brand name companies also reach agreements with generics manufacturers in order to reduce competition. The Federal Trade Commission (“FTC”) filed numerous antitrust suits against brand name manufacturers, alleging that they had paid generic manufacturers millions of dollars to delay or kill entry of generic products.¹¹⁴ As of 2002, the FTC had challenged three settlement agreements between generic and brand name manufacturers in which brand name manufacturers paid the generic applicant that had a 180-day exclusivity under Hatch-Waxman not to enter the market, thereby ensuring that no generic would enter the market for the exclusivity period.¹¹⁵ This practice was the subject of successful antitrust suits and Congress recently prohibited it by enacting legislation mandating forfeiture of the 180-day exclusivity, triggered by events which indicate collusive agreement between first-filer generic and brand-name drug. However, brand name manufacturers can still license a single generic drug during the patent term or produce its own generic version of the drug.¹¹⁶ The presence of these “branded generics” reduces the value of the six-month exclusivity period for the first paragraph IV challenge under Hatch-Waxman and thereby deters additional generic competition after the patent term expires.¹¹⁷ Although the marketing of branded generics may mean that a generic version reaches the market a few months sooner, it also means that a competitive market for the original drug develops more slowly after patent expiration.

Brand name drug manufacturers have also prevented promising research by controlled entities when such

¹¹³Adams, *Drug Makers Face Battle to Preserve Patent Extensions*, *supra* note 94.

¹¹⁴Harris, *Delayed Reaction: Drug Manufacturers Step Up Legal Attacks That Slow Generics*, *supra* note 103.

¹¹⁵FEDERAL TRADE COMMISSION, *GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION*, *supra* note 96, at vii.

¹¹⁶*See e.g., Teva Pharm. Ind. Ltd. v. Crawford*, 410 F.3d 51 (D.C. Cir. 2005) (upholding FDA denial of generic maker Teva’s request to prohibit the brand name company from marketing a generic version of its drug during Teva’s 180-day marketing exclusivity period).

¹¹⁷These deals are known in the industry as “authorized generics.” Hollister H. Hovey, *Big Pharma Courts Generics’ Rivals*, WALL STREET JOURNAL, Aug. 11, 2004, at 1; Leila Abboud, *FDA Declines to Curb a Tactic of Drug Firms Against Generics*, WALL STREET JOURNAL, Jul. 6, 2004, at C3; Leila Abboud, *Drug Makers Use New Tactic to Ding Generics*, WALL STREET JOURNAL, Jan. 27, 2004, at B1.

research threatens to compete with another established or potential product.¹¹⁸ For instance, Tanox Inc. terminated testing for a promising new peanut allergy medication, TNX-901, in response to pressure from its business partner Genentech, which was developing a medication for the same indication (Xolair).¹¹⁹ Genentech sued to prevent Tanox from continuing clinical trials of TNX-901, citing the commercial threat TNX-901 posed to Xolair, although Xolair was being tested for other indications, not peanut allergies. A lawyer from Genentech argued, “We really need to not have a competing product in the market from our strategic partner.”¹²⁰

I.D. 2. Patent-Based Anti-Generic Tactics (Evergreening)

Brand name manufacturers also have a variety of patent-based tactics for fending off generic competition. During the 1990s, Schering-Plough poured millions of dollars into an unsuccessful lobbying effort to win special congressional approval for a patent extension for Claritin, arguing that delays at the FDA cost Claritin years of sales.¹²¹ However, a far more common practice has been the use of strategies for maintaining market share through the manipulation of existing patent law and its interaction with the Hatch-Waxman Act. These practices are collectively known as “evergreening” because they have the effect of extending the patent term for a brand name drug. As one patent nears expiration, new patents on features of the drug issue and delay generic competition further. Evergreening is typically accomplished by patenting modifications of an already-patented product at the end of its patent life. Each new patent can be used as the basis of

¹¹⁸ See e.g., David P. Hamilton, *Silent Treatment: How Genentech, Novartis Stifled A Promising Drug; Biotech Firm Tried to Pursue Peanut-Allergy Injection, But Contract Got in Way; Zach Avoids a 'Kiss of Death'*, WALL STREET JOURNAL, Apr. 5, 2005, at A1.

¹¹⁹ *Id.*

¹²⁰ *Id.*

¹²¹ Gardiner Harris, *Leading the News: Schering-Plough Loses Defense Involving Claritin*, WALL STREET JOURNAL, Aug. 9, 2002, at A3; Patent Fairness Act of 1999, H.R. 1598, 106th Cong. (proposing to extend patent for Claritin) (cited in Dan L. Burk and Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1631, fn186, (2003)).

a lawsuit against generic manufacturers, and its own patent extension and market exclusivity period under Hatch-Waxman. In conjunction with market failures in pharmaceutical markets, this can mean that the reward that a manufacturer derives from a modification patent can far exceed its value to society.

The patent law provides some protection against this practice. In order to issue, a patent must be novel and nonobvious.¹²² This means that a patent applicant is precluded from obtaining a patent on an invention that has been patented previously or has been in public use, and from obtaining a patent on an obvious modification of a previously-patented drug (*see* “Prevention of Double Patenting,” Part III.B, *infra*). In the absence of Hatch-Waxman, it is difficult for a patent that is likely to be invalid for obviousness or lack of novelty to retard competition, since the patent holder would have to convince a court to issue a preliminary injunction against a competitor and would therefore have to be able to make a colorable claim that the patent is valid. Hatch-Waxman, however, grants the patent holder an automatic 30-month ($2\frac{1}{2}$ year) stay on the approval of a generic that is not reviewed by a court. Thus, even a patent likely to be invalidated by a court can significantly delay generic entry.¹²³ Prior to the 2003 Amendments to Hatch-Waxman, manufacturers used multiple patent listings to generate successive $2\frac{1}{2}$ year stays on generic entry. This practice is no longer possible, but listing multiple patents to protect a single brand name drug can still benefit the manufacturer by increasing the time and complexity of infringement litigation.¹²⁴ Thus, the Hatch-Waxman mechanism reverses the patent holder’s incentives in litigation. Whereas usually a patent holder would want to resolve the legal issue of patent validity quickly so as to receive court-ordered remedies for infringement, under Hatch-Waxman, the plaintiff brand-name manufacturer benefits from drawn-out litigation. Even a patent which is likely to be declared invalid by a court and for which the plaintiff will be awarded no damages relief

¹²²15 U.S.C. §102, 103 (2006).

¹²³Artie Rai, *Symposium of Bioinformatics and Intellectual Property Law, April 27, 2001 – Boston, Massachusetts: The Proper Scope of IP Rights in the Post-Genomics Era*, 8 B.U. J. SCI & TECH. L. 233, 238-39 (2002); *but also see* FEDERAL TRADE COMMISSION, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION, *supra* note 96, at v. (The FTC is aware of a few cases in which a 30-month stay was generated by a patent that raised legitimate questions about whether its listing was appropriate).

¹²⁴FEDERAL TRADE COMMISSION, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION, *supra* note 96, at 40, 47. (data showing that suits involving multiple patents take longer to resolve than those involving fewer patents).

generates substantial value for its holder.

Given the incentives Hatch-Waxman produces, it is not surprising that the average number of patents protecting brand-name drugs has increased from two to twelve over the past ten years, and the number of patents for a particularly profitable drug may far exceed this average.¹²⁵

These patent- and non-patent-based strategies give brand name drug manufacturers many tools for reducing competition and increasing revenues, such that the manufacturer's exclusive hold on a market is extended beyond the statutory period of the controlling patent. The question then for policy-makers is whether the rewards that a patent confers, which may be extended at least in part well beyond the statutory term, set the right balance between competition and public subsidization. The increase in rewards generated by these strategies is easiest to justify for drugs whose social benefits greatly exceed social costs (including the costs associated with monopoly pricing); and indeed, availability of these strategies is arguably needed to create incentives for important innovations. However, as discussed in Part II. A., *infra*, the availability of these strategies also creates perverse incentives for the pharmaceutical industry that reward incremental innovation far in excess of its net social value.

II. INCREMENTAL INNOVATION

II. A. The Case Against Incrementalism

While pharmaceutical manufacturers defend the revenues generated by new medications as reflecting the value they provide to the public, critics of the industry argue that many of the newly-patented drugs are

¹²⁵Gardiner Harris and Joanna Slater, *Bitter Pills: Drug Makers See 'Branded Generics' Eating Into Profits — Altered Copies Outmaneuver Patents in Legal Battles, Boosting Market Pressures — Dr. Reddy's Finds a Loophole*, WALL STREET JOURNAL, Apr. 7, 2003 at A1.

insignificant improvements over products already on the market.¹²⁶ Thanks to market failures, some of these insignificantly improved drugs have become blockbusters, which generate billions of dollars in revenue. A recent report by Blue Cross's National Institute for Health Care Management Research and Educational Foundation ("NIHCM") concluded that there is a substantial disparity between spending and clinical value, since a large increase in recent spending is attributable to product line extensions providing no significant clinical improvement over older medications.¹²⁷

The arguments against incrementalism in pharmaceutical research are twofold: first, the direction of resources toward incremental innovation retards the development of break-through innovation by diverting resources away from more ambitious projects; and second, it reduces access to needed medicines without significantly improving quality of care.

II. A. 1. Distortion of Incentives

Since it requires an investment of hundreds of millions of dollars to develop a marketable product, the availability of large rewards for incremental innovations creates an economic incentive to divert resources towards incremental improvements, since this increases the likelihood of realizing commercial benefit. Modification of a drug whose safety and efficacy are known is far less risky and expensive than developing a completely new chemical entity. This combination of lower risk and high prices allowed by the combination of patent protection, marketing exclusivity, faster FDA approval of new versions of already-marketed drugs, and the price insensitivity of physicians and insured consumers combine to create powerful financial incen-

¹²⁶See e.g., Marcia Angell, *THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT*, 2004; Relman, *America's Other Drug Problem*, *supra* note 52.

¹²⁷THE NATIONAL INSTITUTE FOR HEALTH CARE MANAGEMENT, RESEARCH AND EDUCATIONAL FOUNDATION, *Changing Patterns of Pharmaceutical Innovation*, *supra* note 106, at 19-20.

tives for modest innovations.¹²⁸ Under pressure from investors for annual revenue growth and facing patent expirations for blockbuster drugs, pharmaceutical manufacturers no doubt face strong pressure to develop commercially successful products as rapidly as possible. Dr. Sharon Levine, the associate executive director and a pediatrician for the Kaiser Permanente Medical Group, speaking on ABC News framed the question thus:

If I'm a manufacturer and I can change one molecule and get another 20 years of patent rights, and convince physicians to prescribe and consumers to demand the next form of Prilosec, or weekly Prozac, instead of daily Prozac, just as my patent expires, then why would I be spending money on a lot less-certain endeavor, which is looking for brand-new drugs?¹²⁹

As evidence that incrementalism is becoming more common, critics of the industry point to the decreasing number of NDAs issued for new chemical entities (“NCEs”). The FDA’s classification of NDAs provides a useful starting point for considering which pharmaceutical products are most valuable. The FDA classifies NDAs along two dimensions: chemical type and therapeutic potential.¹³⁰ To classify by chemical type, the FDA identifies each NDA as falling into one of six categories. NCEs are compounds which have never been approved for marketing in the U.S. Another four categories describe chemicals modification of a drug whose active ingredient is already on the market. These include new esters, salts or noncovalent derivatives, new formulations, new combinations with other already marketed drugs, and new indications. NIHCM refers to these categories collectively as “incrementally-modified drugs” (“IMDs”).¹³¹ The FDA also has categories for applications for an already-marketed drug by a new manufacturer and for already-marketed drugs without an approved NDA. NIHCM refers to these as “other drugs.”¹³²

¹²⁸*Id.*, at 4.

¹³⁰THE NATIONAL INSTITUTE FOR HEALTH CARE MANAGEMENT, RESEARCH AND EDUCATIONAL FOUNDATION, *Changing Patterns of Pharmaceutical Innovation*, *supra* note 106, at 2.

¹³¹*Id.*

¹³²This system of categorization is very similar to the NIHCM report; however, since they do not describe precisely which FDA categories fall into “IMDs” and “Other,” this system may vary slightly. The number of drugs that fall into the “other” category comprises a very small percentage of the total, so these results should be very close to those that the NIHCM methodology would produce.

The FDA also categorizes each NDA as either “standard review” or “priority review,” based largely on its therapeutic potential. This classification of NDAs is intended to enable the FDA to direct its resources towards reviewing applications for drugs that show the greatest potential for therapeutic advance.¹³³ Specifically, the FDA assigns a drug to the priority review category if the drug manufacturer offers evidence of increased effectiveness relative to products on the market, elimination or substantial reduction of side effects and interactions, enhanced patient compliance or use in a new subpopulation.¹³⁴ All other NDAs are classified as “standard.” The FDA policy states that to receive priority rating, the NDA must provide evidence that it is a “significant” improvement over drugs already on the market.¹³⁵ Products that are rated as “standard” then are generally products for which significant improvement cannot be shown. Notably, however, the purpose of the FDA rating structure is to allow it to prioritize its work, so the definition of “priority” is not necessarily fixed over time. Rather, the rating an NDA receives probably also reflects the urgency of other concurrent submissions from the industry. If the industry submitted primarily NDAs for drugs that were of little marginal benefit relative to existing drugs and the FDA rated them all “standard,” then the rating system would lose its value as a management tool.¹³⁶

The NIHCM report *Changing Patterns of Pharmaceutical Innovation*, categorizes drugs according to their degree of innovation based on the two FDA classifications. This classification system is shown in Table 3, *infra*. As a rough measure of innovation, these categories are useful for examining the trends in pharmaceutical innovation that are revealed by FDA data.

Table 3: NIHCM Classification by Degree of Innovation

Degree of Innovation	Classification	Description
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¹³³Center for Drug Evaluation and Research, FDA, MANUAL OF POLICIES AND PROCEDURES 6020.3, 1996, at 2.

¹³⁴*Id.*, at 1-2.

¹³⁵*Id.*, at 1.

¹³⁶DiMasi, *The Economics of Follow-On Drug Research and Development*, *supra* note 86, at 8.

Greatest	Priority NCE	Break-through drug
	Standard NCE	Usually have same mechanism of action as an already-marketed drug, but may have a different safety and efficacy profile that provides benefits to a subpopulation

	Priority IMD	New form of drug (whose ac- tive in- gre- di- ent is al- ready mar- keted) with im- proved safety or ef- fec- tive- ness rel- a- tive to oth- ers in the ther- a- peu- tic class
	Standard IMD	Enhances patient choice and convenience

Least	Other	Not in- no- va- tive: drugs that were on the mar- ket be- fore Congress en- acted the Kefauver- Harris Drug Amend- ments in 1962
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Table 4, *infra*, illustrates trends in approvals over time. These data indicate that while drug approvals increased during the 1990s, most of the growth was in standard IMDs (100 out of the additional 157 NDAs); and that while total drug approvals have declined in recent years, approvals of IMDs have remained steady. Furthermore, priority NCEs account for only 11% of newly approved drugs, but they account for nearly half of the total decline in approvals.

Table 4: Trends in NDA Approval by Degree of Innovation¹³⁷

¹³⁷Data are from Center for Drug Evaluation and Research, FDA, *NDAs Approved in Calendar Years 1990-2004 by Therapeutic Potential and Chemical Type*, available at <http://www.fda.gov/cder/rdmt/pstable.htm>. Also see NIHCM for analysis of trends

	1990-1994	1995-1999	2000-2004
Priority NCEs as % of NDAs	14%	18%	11%
Total Priority NCEs	90	117	80
% Change		+30%	(32%)
Standard IMDs as % of NDAs	39%	49%	58%
Total Standard IMDs	139	249	247
% Change		+78%	(1%)
Total NDA Approvals	350	507	427
% Change		+45%	(16%)

Other data support the apparent slowdown in pharmaceutical innovation.¹³⁸ The *New York Times* recently reported that despite record investment in R&D by the pharmaceutical industry, new drug approvals by the FDA declined in 2005 relative to 2004.¹³⁹ Some observers argue that the pharmaceutical industry has responded to the financial incentives inherent in the current regulatory framework by focusing more of their efforts on incremental innovation.¹⁴⁰ In addition, there is evidence that identifying break-through drugs has

in 1989-2000 data. THE NATIONAL INSTITUTE FOR HEALTH CARE MANAGEMENT, RESEARCH AND EDUCATIONAL FOUNDATION, *Changing Patterns of Pharmaceutical Innovation*, *supra* note 106.

¹³⁸The current slowdown is not a new phenomenon, however. In the 1970s, industry observers expressed concern about the declining levels of new introductions and speculated that the industry had entered a mature phase with diminished opportunities for innovation. This concern provided some of the impetus for the Hatch-Waxman Act of 1984. In 1982, former FDA Chief Counsel Peter Barton Hutt testified on behalf of PhRMA that the pace of innovation was declining and that enhanced patent protection was necessary to spur increased investment in R&D. Peter B. Hutt, *The Importance of Patent Term Restoration to Pharmaceutical Innovation*, HEALTH AFFAIRS, Spring 6 (1984).

¹³⁹Alex Berenson, *Drugs in '05: Much Promise, Little Payoff*, NEW YORK TIMES, Jan. 11, 2006, at C1.

¹⁴⁰Relman, *America's Other Drug Problem*, *supra* note 52, at 30-33.

become more technically difficult in recent years. The proportion of drugs investigated that eventually reach the market shows a downward trend. Bain Consulting found that the number of drugs that enter animal testing which subsequently make it to market has declined from 1 in 8 in the 1995-2000 period to 1 in 11 in the 2000-2002 period.¹⁴¹ Thus, the trend toward incremental innovation may be exacerbated by technical challenges that reinforce regulatory incentives for incrementalism.

Alternative theories as to the causes of the recent slowdown abound. Some industry analysts argue that the revolution in genetic engineering is slowing drug development, as companies need time to develop so many complicated new tools.¹⁴² Others blame organizational structures in large companies that impede innovation.¹⁴³ For example, *The New York Times* reported that Glaxosmithkline's labs were "virtually paralyzed by a post-merger reorganization."¹⁴⁴ Pharmaceutical mergers have resulted in larger companies that may be less willing to take risks. As a result of mergers, projects may be stopped, not for lack of merit, but because they are too small (in terms of potential market) or do not fit within the merged company's business strategy.

Although the pharmaceutical industry has expressed considerable concern that price controls would cripple innovation, no significant price controls have materialized yet, and the current slowdown has not been attributed to downward pressure on prices.

These trends towards incrementalism are concerning to the extent that they suggest that more innovative research is being crowded out. The FDA data do not reveal the reasons that the rate of break-through

¹⁴¹Landers, *Cost of Developing a New Drug Increases to About \$1.7 Billion*, *supra* note 68.

¹⁴²"Looking forward, the drug industry is currently confronted with a new wave of technological opportunities. The mapping of the genome and related advances in fields such as bioinformatics have led to an abundance of potential new targets for disease intervention.... A recent report by Lehman Brothers foresees a negative impact on returns until at least the latter part of this decade, when the substantial required buildup in R&D investments should begin to bear fruit." Grabowski, *Returns on Research and Development for 1990s New Drug Introductions*, *supra* note 77, at 26.

¹⁴³Mallorye Branca, *Genomics Provides the Kick Inside*, BIO IT-WORLD, available at <http://www.bio-itworld.com/archive/111403/horizons.kick.html>.

¹⁴⁴*Id.*

innovation has declined recently, but they are at least consistent with the hypothesis that market failures and current regulatory structures create greater incentives for incremental research than for more innovative efforts.

II. A.2. Consumer Access Limited by Pricing

Incremental improvements are also concerning to the extent that they increase social costs in excess of their social benefits. While precise cost-benefit analyses are prohibitively complex, it is at least clear that incremental improvements are substantial cost drivers. New standard-rated drugs accounted for \$29.3 billion in increased drug spending from 1995-2000 and 67% of the total increase in spending.¹⁴⁵ Although the existence of substitutes for a drug should theoretically drive prices down, the moral hazard associated with insurance and marketing by manufacturers may increase the patient population for a particular drug above efficient levels and prevent customers from migrating to the most cost-effective option.¹⁴⁶ Insured patients typically do not face the entire price of the drug they are receiving and thus do not face a strong incentive to shop for the lowest-cost option. Accordingly, incremental innovations usually do not result in significant reductions in the price of pioneer drugs, because they are imperfect substitutes, and insured patients and doctors who are insensitive to price tend not to respond to imperfect substitution.¹⁴⁷ Moreover, patients who are price insensitive are highly susceptible to advertising.¹⁴⁸ This allows drug manufacturers to make tremendous profits from drugs that are true improvements only for a small subset of patients. Thus, though an IMD may provide a marginal net benefit for a small proportion of patients, the total marginal benefit

¹⁴⁵THE NATIONAL INSTITUTE FOR HEALTH CARE MANAGEMENT, RESEARCH AND EDUCATIONAL FOUNDATION, *Changing Patterns of Pharmaceutical Innovation*, *supra* note 106, at 11.

¹⁴⁶See Swidey, *The Costly Case of the Purple Pill*, *supra* note 8.

¹⁴⁷Rai, *Symposium: Intellectual Property Challenges in the Next Century: The Information Revolution Reaches Pharmaceuticals: Balancing Innovation Incentives*, *supra* note 56, at 206.

¹⁴⁸*Id.*

is likely to be small relative to the total marginal cost, particularly when the new drug addresses illnesses whose symptoms are fairly mild, like allergies.¹⁴⁹

II. B. The Case for Incrementalism

Some industry observers argue that incremental innovations are socially valuable and that patent law should encourage them. Advocates for strong patent protection of incremental innovations make three major arguments in favor of them. First, they argue that the class of incremental innovations which are commonly derided as “me-too” drugs are in fact important technical advances, which produce both medical and economic benefits. “Me too” drugs were first identified as a problem in the U.S. Senate (“Kefauver”) hearings in the late ‘50s and early ‘60s. A “me too” drug is a new drug entity with a similar chemical structure or the same mechanism of action as that of a drug already on the market. Often, it is a new member of a therapeutic class of drugs that has been identified by another drug entity that was first in its class, the “pioneer” drug.¹⁵⁰ “Me too” drugs are less controversially known as “follow-on” drugs.

Studies by DiMasi and Paquette challenge the assertion that the pioneer drug is usually the best in its therapeutic class. Fifty-seven percent of all therapeutic classes have at least one follow-on drug that received a priority rating. The pattern of innovation DiMasi and Paquette uncovered suggests a development race for drugs in a new therapeutic class, rather than a scenario in which firms engage in low-risk imitation of a proven break-through.¹⁵¹ Nearly all follow-on drugs for classes where a pioneer drug was approved in the 1990s were in clinical trials before the pioneer drug was approved.¹⁵² Thus, DiMasi and Paquette conclude

¹⁴⁹ *Id.*, at 205-6.

¹⁵⁰ DiMasi, *The Economics of Follow-On Drug Research and Development*, *supra* note 86, at 2.

¹⁵¹ *Id.*, at 10.

¹⁵² *Id.*, at 9.

that

[t]he prevailing drug development paradigm is one in which a number of firms will pursue investigational drugs with similar chemical structures or the same mechanism of action before any drug in the class obtains regulatory marketing approval.... Thus, the typical drug development model is one in which firms are, in effect, engaged in development races, as opposed to one that is characterized by after-the-fact imitation.¹⁵³

Furthermore, they argue that the discovery of multiple drugs in the same class is beneficial because they differ in their side effects, average efficacy, efficacy in particular individuals, adverse reactions, drug-drug interactions, dosing schedules and delivery systems.¹⁵⁴ DiMasi and Paquette's research also indicates that the presence of multiple drugs in a therapeutic class introduces some price competition.¹⁵⁵

Advocates of strong patent protection also contend that even drugs that are not shown to be safer or more efficacious than already-marketed drugs have important health benefits. In testimony before the Subcommittee on Investigations and Oversight of the House Committee on Science and Technology, Peter Hutt argued on behalf of PhRMA that drugs that are no better on average than those already on the market nevertheless provide substantial value to patients:

Whoever argues that a drug offers little or no therapeutic advantage is talking about an average over millions of people, not about a single patient. A drug that seems to offer little therapeutic advantage to the entire population may well be, and often is, the only drug that offers any therapeutic benefit to a small subpopulation. And if you happen to be one of the individuals in that subpopulation, that particular drug has an enormous therapeutic advantage, rather than the small therapeutic advantage attributed to it by others. Indeed, for you it is the only important drug. Classification of a drug as important or unimportant is therefore arbitrary and ignores the specific needs of individual patients... the availability of a wide variety of drugs for any particular disease is... vital to the public health.¹⁵⁶

The benefit of having a variety of medications available for a particular indication, however, is limited by the amount of data available to physicians about the relative advantages of a drug for certain subpopulations.

While it is certainly true that a drug which is less effective for the general population may be better for

¹⁵⁴ *Id.*, at 11.

¹⁵⁵ *Id.*, at 12. *But see* Rai, *Symposium: Intellectual Property Challenges in the Next Century: The Information Revolution Reaches Pharmaceuticals: Balancing Innovation Incentives*, *supra* note 56, at 206.

particular individuals, drug manufacturers are not required during the patent application process or the FDA approval process to provide the public with any information about who those individuals might be.

A third important argument for encouraging incrementalism stems from the nature of biomedical research. Technological advances in biomedical research are more commonly achieved through a series of incremental steps rather than isolated break-throughs.¹⁵⁷ If all advance is incremental and break-throughs are usually random results of incremental research, then policies should be designed to promote a large population of incremental research projects from which a break-through innovation may emerge. Furthermore, the prospect of follow-on incremental products may provide necessary incentives for break-through innovation if the current patent term is not an adequate reward itself for break-through innovation.

II. C. Categories of Incrementalism

The extraordinary profitability of drugs like Nexium, which are not significant improvements over less expensive drugs already on the market, suggests that current patent and regulatory law rewards incremental improvements far in excess of their actual value to society. Concomitantly, data showing the extraordinary cost of break-through innovation suggests that rewards for it may be too low. This mismatch of benefit and reward should be of particular concern for the development of patent law, given that the justifications for the award of patents are fundamentally utilitarian. The background assumption in American patent law is that free competition generates the greatest social good, and that exceptions should be made to this rule only where the benefits of limiting competition exceed costs. Labor and desert theories of property law play only a secondary role in justifying patent law. The primary goal of the patent law is not to reward inventors

¹⁵⁷Albert Wertheimer, Thomas W. O'Connor, Jr., and Richard Levy, THE VALUE OF PHARMACEUTICAL INNOVATION FOR OLDER AMERICANS 3 (2001) available at http://www.npcnow.org/resources/PDFs/valueincremental_pharm_olderamericans.pdf.

with what they deserve as a matter of natural right. Indeed, Thomas Jefferson, one of the early drafters of American patent law, argued that “[s]ociety may give an exclusive right to the profits arising from them, as an encouragement to men to pursue ideas which may produce utility, but this may or may not be done according to the convenience of society...”¹⁵⁸ Since the goal of patent law is to encourage societal goals, patent policy should be tailored to achieve these goals.

As a preliminary step in analyzing the effectiveness of the current patent regime in promoting innovation, it is important to consider what kinds of innovations should be considered valuable to society and which are less valuable; and then to consider whether the patent law under-incentivizes the most valuable innovations and/or over-incentivizes the least valuable.

Clearly, the main rationale for the subsidization of the pharmaceutical industry through the patent system is to produce health benefits, so the extent to which a drug improves health should be one measure of its value. The degree to which such improvements are realized will necessarily depend not only on the properties of the drug itself but on the amount of information which researchers provide to locate the population for whom it provides a health benefit. A drug may have the same effect as an already-marketed drug in most people, but be significantly better for a subpopulation with a particular genetic or biochemical profile. To the degree that this subpopulation is identified in clinical trials, physicians are able to efficiently target those medications to the population for whom they are effective, instead of proceeding by an inefficient process of trial and error with each patient. Any classification of social benefit then must take into account not only improved properties of drugs, but also enhancements in the knowledge available for physician decision-making.

A one-dimensional scale that takes into account both factors (product properties and knowledge) is difficult to construct with precision. I have attempted to develop a scale that roughly prioritizes the social benefit of

¹⁵⁸Thomas Jefferson, Letter to Isaac McPherson, Aug. 18, 1813 (cited in ROBERT P. MERGES AND JANE C. GINSBURG, FOUNDATIONS OF INTELLECTUAL PROPERTY LAW, 2004, at 19).

both types of improvement, but it is necessarily imprecise. Table 6, *infra*, shows a possible ordering of general categories of innovations. For the sake of simplicity, this scale does not differentiate between drugs used to treat serious versus less serious disease or common versus rare disease, although these are also important considerations.

Another useful measure is the difficulty of discovery, as this would be a rough indicator of the degree of incentive that the patent system needs to provide beyond market incentives. The nonobviousness requirement of patent law itself suggests a framework for analyzing difficulty of discovery. Under the patent statute, no patent may issue if “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.”¹⁵⁹ Even an invention that is novel in the literal sense of the term, is not patentable if “its contours are so traced by the existing technology in the field that the ‘improvement is the work of the skillful mechanic, not that of the inventor.’¹⁶⁰ Thus, the nonobviousness standard tries to measure the degree of technical advance over already-existing inventions to determine whether it is worth rewarding with patent protection.

In the context of chemical inventions, the Federal Circuit has rejected a potential definition of obviousness that encompasses inventions that result from an “obvious approach to try.”¹⁶¹ A chemical product is not rendered obvious merely because the prior art suggests that it might be a logical target for investigation as a drug. An investigation of a chemical that is “obvious to try” might involve substantial risk of failure, and therefore require incentives to encourage in the absence of any expectation of success. Under current doctrine, the absence of “reasonable expectation of success” is an indicator of nonobviousness. Thus, an obvious *result* is needed to render the invention obvious. The nonobviousness analysis considers “(1) whether

¹⁵⁹35 U.S.C. §103 (2006).

¹⁶⁰*Bonito Boats v. Thunder Craft Boats*, 489 U.S. 141, 149-50 (1989) (quoting *Hotchkiss v. Greenwood*, 11 How. 248, 267 (1851)).

¹⁶¹See e.g., *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987) (PTO failed to establish a *prima facie* case of obviousness since at best “one skilled in the art might find it obvious to try various combinations of these known” elements).

the prior art would have suggested to those of ordinary skill in the art that they should make the claimed [invention]; and (2) whether the prior art would have suggested to those of ordinary skill in the art that in so making... those of ordinary skill would have *a reasonable expectation of success*.”¹⁶²

This differentiation of innovations in case law into “obvious to try” and “obvious result” suggests one way of characterizing the degree of innovation. One might classify a new drug as either innovative, obvious to try (such as additional members of a therapeutic class), or an obvious result that the average pharmaceutical researcher could foresee (such as applying a well-known delivery method to a known drug). The degree of innovation required would then suggest whether such discoveries are appropriate targets for the incentives provided by patents. However, the degree of innovation and degree of social benefit should not be conflated. Some significant innovation results from ideas that are “obvious to try” (e.g. a purified stereoisomer that works better than its racemate), but new compounds that provide little social benefit also result from ideas that are “obvious to try” (e.g., Nexium). Thus, whether something is “obvious to try” does not indicate whether the invention is socially beneficial.

The resulting classification system is summarized in Table 5, *infra*, and a possible classification of types of drug discovery using this system is illustrated in more detail in Table 6, *infra*.¹⁶³

Table 5: Classification of Drugs by Social Benefit and Inventiveness

	Net Social Benefit	
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¹⁶²*In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

¹⁶³The category labeled “innovative” corresponds with the colloquial meaning of “not obvious” but I have avoided that term here so as not to confuse it with its more specific meaning in the context of patent law.

Difficulty of Discovery / Degree of Innovation	Insignificant				Low	Substantial
Obvious to Try	<i>Least justification for patent protection</i>					
Obvious Result						
Innovative						

	<i>Social Benefit</i>			
	<i>Insignificant</i>	<i>Low</i>	<i>Substantial</i>	<i>Great</i>

Difficulty of Discovery / Degree of Innovation	No new knowl- edge or product	Increased knowl- edge of safety/efficacy for a known sub- pop- u- la- tion	Potential im- proved safety/efficacy for un- known sub- pop- u- la- tion (ex- pands op- tions)	Improved pa- tient com- fort / con- ve- nience - > im- proved pa- tient com- pli- ance /ef- fi- cacy	Improved safety/efficacy for known sub- pop- u- la- tion	Reduced risk of rare side ef- fects for en- tire pop- u- la- tion (mor- tal- ity/ mor- bid- ity)
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Obvious Result	New use for a known drug which is already being used off-label for the new use - could be in the “substantial” category if the maker has to submit an NDA (Neurontin)			Combination of known ingredients that yield expected results (Allegra ‘974, Prilosec, Claritin)	Known route/method of administration applied to known drug			New application of known pill coating method (Prilosec)	New and expected use for a known drug	
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Obvious to Try	Natural metabolite	Identify additional benefits to sub-population of population in which drug is already known to be safe and effective (Allegra '353)	Purified metabolite Stereoisomer that is more effective or safer than race-mate in an identified sub-population (Nexium)	Purified metabolite (Clarinox)	Stereoisomer that is more effective or safer than race-mate in an identified sub-population	New formulation to reduce toxicity (Neurontin) Stereoisomer that is more effective or safer than race-mate	Studies generating additional knowledge about off-label and approved uses	New chemical entity in known therapeutic class	
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Innovative				Chemical change to allow new route/method of administration (Aranesp)		
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Greatest Net Social Benefit

The justification for patent protection is strongest for those drugs that fall into the category of greatest social benefit and greatest degree of innovation. In this category of inventions, the paradigmatic cases are new chemical entities that establish a new therapeutic class, new and unexpected uses for known drugs, and combinations of known drugs that yield unexpected therapeutic effects. For example, fluoxetine (Prozac), the first marketed selective serotonin reuptake inhibitor, and omeprazole (Prilosec), the first proton pump inhibitor, would fall into this category. These drugs were revolutionary advances over existing therapies and suggested future direction for fruitful investigation. Investigation of compounds that are structurally similar to the pioneers in a therapeutic class can be classified as “obvious to try” but since the biological activity of compounds is not easily predicted from structure, they are not obvious to succeed. As discussed in Part II.B., *supra*, though less purely innovative, later-discovered compounds in a known therapeutic class may be safer and more effective than the pioneer drug.

An unexpected use of a known drug or a combination of known drugs that yields unexpected results would include only inventions whose efficacy did not seem all but certain given the state of knowledge about its uses at the time of invention. This would therefore likely require significant inventive effort and costly research to identify.

Some inventions may produce great social benefit through increased efficacy, but require little inventive effort. This category of invention includes the discovery of new and expected uses for known drugs. In these cases, the biological mechanism of related diseases may be so closely related that the successful application of a known drug to the new indication would be an obvious result, but nonetheless provide substantial social benefit.

The category of inventions with the greatest social value but the least innovation also includes those in

which real increases in efficacy are achieved by applying well-understood technologies in new contexts so as to achieve a predictable result. For example, AstraZeneca received a patent for putting two coatings on the active ingredient of Prilosec.¹⁶⁴ Prilosec's active ingredient does not survive long, and so it needs to be coated so the active ingredient lasts long enough to be absorbed into the intestine. This problem is so common that the problem and its solution are described in standard industry textbooks.¹⁶⁵ If this is the case, there is arguably no need to offer patent protection for the application of known coating methods to a known drug, since there are sufficient market incentives for manufacturers to apply existing technologies to ensure that their pills are effective.

Substantial Net Social Benefit

Other pharmaceutical developments that generate important social benefits include 1) studies that increase knowledge of safety and efficacy, 2) modifications of existing drugs which improve over prior drugs by exhibiting lower rates of unwanted effects, 3) drugs which are improvements over prior drugs in terms of safety and efficacy for a known subpopulation, and 4) improvements to drugs that increase patient comfort and convenience.

Studies that increase knowledge of safety or efficacy would provide support to approved and off-label uses. Such studies would not produce patentable products or uses, since they would likely fail the requirement of novelty. However, they nonetheless produce important social benefits in the form of knowledge to guide patient and physician decision-making.

New drugs that improve over existing drugs by reducing side effects can also generate important social benefits. This would include new formulations of known active ingredients with chemicals that reduce degradation

¹⁶⁴Harris, *Drug Prices – Why They Keep Soaring*, *supra* note 2.

¹⁶⁵*Id.*

and toxicity and changes to the compound that allow for less frequent administration or a less invasive route of administration. For example, the maker of best-selling drug Epogen chemically modified it, so that it would have a longer half-life and thus require less frequent administration.¹⁶⁶

Another important and controversial category of improvements that potentially falls into this category is the development of purified stereoisomers. The formation of stereoisomers occurs in about half of all drug compounds.¹⁶⁷ They are mirror image forms of the same chemical compound. They have identical chemical formulas and connectivity between atoms, but differ in their three-dimensional structures. Although stereoisomers have identical physical properties (other than optical activity), they have unique biological effects, since many biochemical reactions depend on a lock-and-key interaction that is dependent on three-dimensional structure.¹⁶⁸ Since many biochemical reactions use a particular three-dimensional form of a drug, but not its stereoisomer, the two or more stereoisomers of a compound may have profoundly different effects on biological systems. In some cases, one stereoisomer has a therapeutic effect, while the other is toxic. Given these important differences, a purified active stereoisomer may be a significant improvement over a drug that was originally produced as a mixture of stereoisomers (also known as a “racemate” or “racemic” mixture).¹⁶⁹

Stereochemistry has been known since Louis Pasteur identified the phenomenon in the 19th century and its effects on the biochemical activity of pharmaceuticals has been well-understood for decades. In the 1990s, economical methods of developing pure stereoisomers became widely available.¹⁷⁰ Thus, improving a known

¹⁶⁶Medical Officer Clinical Review, Center for Drug Evaluation and Research, FDA, ARANESP MEDICAL REVIEW. CLINICAL REVIEW OF BLA 99-1492/ STN103951, Sept. 5, 2001 at 6, available at http://www.fda.gov/cder/biologics/review/ARANESP_Med_Officer_Review.pdf.

¹⁶⁷Michael Strong, *FDA Policy and Regulation of Stereoisomers: Paradigm Shift and the Future of Safer, More Effective Drugs*, 54 FOOD DRUG L. J. 463, 467 (1999).

¹⁶⁸FDA, FDA'S POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS, May 1, 1992, available at <http://www.fda.gov/cder/guidance/stereo.htm>. Physical properties include melting point, boiling point and density. Biological properties refer to the molecules' interaction with chemicals in living organisms.

¹⁶⁹Strong, *FDA Policy and Regulation of Stereoisomers*, *supra* note 167, at 470-71; Steven C. Carlson, *The Case Against Market Exclusivity for Purified Enantiomers of Approved Drugs*, 1 Yale Symp. L. & Tech. 6 (1999) (see Seldane example).

¹⁷⁰Strong, *FDA Policy and Regulation of Stereoisomers*, *supra* note 167, at 467-68.

drug by identifying the stereoisomer which produces its therapeutic effects is “obvious to try,” but the biological activity of an isolated stereoisomer is not predictable from information about the mixture.¹⁷¹ To the extent that researchers show that a purified stereoisomer is more effective and safe than the mixture of stereoisomers, such studies yield important social benefits. Even in cases in which the purified stereoisomer shows no improvements in overall safety and efficacy relative to a mixture, it is possible that the purified form will be safer or more effective in a particular subpopulation of patients. In such cases, the production of the clinical trial data to identify such a population (through the use of head-to-head trials against the mixture) is itself beneficial. Purified stereoisomers would then seem to fall into the category of “obvious to try” but not “obvious result.”

Some inventions which offer significant social benefit, however, are an “obvious result” of uses of prior art. These inventions include combinations of known ingredients that yield expected results. For example, when outside researchers discovered that ulcers were often the result of bacterial infection, AstraZeneca patented the combination of its already-patented drug Prilosec with antibiotics. Combining the two medications in a single pill arguably increases patient convenience, but if the combination yields the same therapeutic results as the two compounds administered separately, then the inventive effort required is minimal.

Another such category of inventions involves the application of well-known routes and methods of administration to known drugs. For example, technologies to allow extended release versions of known drugs can generate important benefits to patients who prefer fewer administrations and may experience fewer side effects. Extended release drugs, for instance, which reduce alcohol dependence or mental illness may help patients achieve significantly better compliance than a daily dose medication, since a weekly or monthly dose does not give the patient a daily chance to change his mind about his therapy.¹⁷² However, the technologies needed to produce this effect may not be innovative. They may involve merely the application of a

¹⁷¹*Id.*, at 472.

¹⁷²See e.g. Rachel Zimmerman, *New Ways to Take Old Drugs Help Patients, Extend Patents*, WALL STREET JOURNAL, Mar. 15, 2004, at B1.

well-known technology to the known compound.

Low Net Social Benefit

Inventions that arguably provide lower benefit than those discussed above include 1) potential for improved safety/efficacy for unknown subpopulation, and 2) increased knowledge of safety or efficacy for a known subpopulation. Some social benefit is derived from studies that identify specific benefits to a subset of a population in which a drug is already known to be safe and effective. For example, Aventis patented its anti-allergen Allegra and later attempted to patent a method for using Allegra as an anti-allergen for patients with impaired liver function. They revealed no new use for the medication, nor was there any change to its chemical formulation. The research they submitted was valuable for what it revealed about the safety of the drug in a particular subpopulation, but did not reveal any new uses for the drug.¹⁷³

Some inventions of purified stereoisomers also produce only minimal social benefit. Pharmaceutical manufacturers have patented purified stereoisomers even when the purified stereoisomer shows no improvement over the mixture of stereoisomers. This is the case for best-selling drugs Nexium (a purified stereoisomer of Prilosec) and Lexapro (a purified stereoisomer of Celexa). Although the purified version does give another option to doctors to use for individual patients who do not react well to the mixture, if no comparative studies are done (none are required for FDA approval), then the inventor has not provided doctors with any information to aid in determining which drug is better for any particular individual. Thus, the availability of these drugs expands the number of options, but they are not necessarily targeted to the patients who would benefit most from them.

The development of purified versions of metabolites of already-marketed drugs is also of low benefit. A

¹⁷³ *Aventis Pharms Inc. v. Barr Labs*, LEXIS 3355, 93 (D.C.N.J. 2006).

metabolite is the chemical product of reactions involving the active ingredient of a drug that take place in the human body, and is the compound that ultimately produces the therapeutic effect (as opposed to the active ingredient in the original drug). Some pharmaceutical companies have developed drugs that consist of the metabolite of a drug already on the market. Some of these metabolites may offer modest benefits over their parent compound, such as a longer half life that allows less frequent administration.¹⁷⁴ Others may provide no average improvement, but provide a benefit to an unknown subpopulation. The metabolite usually produces therapeutic results that are obvious given what is already known about the parent compound. The technical process required to isolate it may not be obvious, so a synthesized metabolite may be only obvious to try, whereas the naturally-produced metabolite would be an obvious result.¹⁷⁵

Insignificant Net Social Benefit

Drug manufacturers have also tried to patent new uses for already-marketed drugs for which it submits no new NDA. If the manufacturer does not provide significant new research to support the efficacy and safety of the drug, its contribution is minimal. For instance, Warner-Lambert patented gabapentin (Neurontin) and patented its use in epilepsy and neurodegenerative disorders. It obtained FDA approval only for use in epilepsy; it did not obtain approval for neurodegenerative disorders. After the product and epilepsy use patents expired, it tried to use the neurodegenerative disorder use patent to bar generic manufacturers from making gabapentin on the grounds that they would induce infringement of its neurodegenerative disorders use patent. This argument was rejected by the Federal Circuit, but nonetheless allowed Warner-Lambert

¹⁷⁴See *e.g.*, Center for Drug Evaluation and Research, FDA, MEDICAL OFFICER REVIEW, NDA 21-165, (2001), available at http://www.fda.gov/cder/foi/nda/2001/21-165_Clarinex_medr_P1.pdf.

¹⁷⁵In *Schering Corp. v. Geneva Pharms, Inc.*, the Federal Circuit invalidated claims for a metabolite of Claritin produced in the human body as inherently anticipated by the patent for Claritin. However, it advised that a metabolite can be patented in its pure and isolated form. 339 F.3d 1373, 1381 (Fed. Cir. 2003).

to obtain a 30-month stay on generic entry.¹⁷⁶ This suggests that patents of new uses which are not then followed-up with research to develop and commercialize the use may even have a negative social value. Although the patent will later be held invalid, the patent owner can, without adding anything new to public knowledge, use a patent which will ultimately be found invalid to delay generic entry and maintain monopoly prices beyond the statutory term of an earlier valid patent.

Implications

As the categories described above emphasize, there is no necessary correlation between the degree of innovation and social benefit to be derived from an invention. Nor given pervasive market failures is there strong correlation between the social benefit of an invention and the rewards reaped by a patent holder. The current regulatory structure thus does not consistently provide the least incentive to low-innovation/low-benefit drugs, or the most incentive to high-benefit/high-innovation drugs. One could imagine addressing this problem by implementing policies which more closely tailor the royalties to be derived from patents to the social benefit the underlying invention produces, and by increasing the standards for patent issuance. The next section explores these possibilities.

III. POLICY LEVERS TO REDUCE INCREMENTALISM

The categories of innovation described in Part II, and the economic and legal context described in Part I, suggest that there are at least two types of errors that lead to under- or over-rewarding innovation in the

¹⁷⁶ *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1359 (Fed Cir. 2003).

pharmaceutical industry. First, the combination of market failures and the low bar for nonobviousness in patent law allows some number of drugs to reap revenues that are far in excess of their benefit. Conversely, in the absence of mechanisms that over-reward follow-on innovations, inadequate incentives may exist for some types of valuable innovation. In other words, manufacturers may not reap adequate returns on their investments in break-through drugs without the additional revenues currently available from follow-on innovation. In order to address this failure, policy-makers need to increase the availability of information available to physicians and patients, so that they can make informed choices about pharmaceutical products. This would likely require a system of mandatory provision of comparative data from independent researchers and government funding for such trials. It might also need to include additional incentives for innovation, possibly in the form of modifications to the marketing exclusivity provisions of the Hatch-Waxman Act.

Second, the interaction of patent law, the Hatch-Waxman Act and other regulatory requirements makes weak patents very valuable to their owners. The importance of preventing the issuance of weak patents in this context means that it is especially important to consider methods of reducing such errors, including revisions to the standards for patentability, improvements to the patent application process, and penalties for double patenting.

III. A. Mis-valued Innovation

The standard account of pharmaceutical innovation argues that pharmaceuticals require strong patent protection because the cost of innovation is exorbitant, whereas the cost of reverse engineering and manufacturing the chemical product is relatively trivial. So, in order to spur continued investment and innovation, the inventor must be given legal assurance that he will be able to appropriate the full value of his invention. The

absence of comparative data about drug effectiveness and safety in conjunction with other market failures, however, has created a system in which patent rewards are poorly tailored to the value of pharmaceutical inventions. One part of the strategy to make patent rewards proportional to the benefit provided by a new drug product should be to increase the payoff for identifying subpopulations for whom drugs are more effective and decrease the payoff for failing to provide such information.

The current state of drug regulation allows manufacturers to market new drugs without having to prove that they are improvements over already existing, less expensive alternatives. The NDA process requires only that the manufacturer show the efficacy and safety of its product relative to a placebo. Voluntary comparative testing is very rare because the risk of results that show no average benefit over existing drugs (and the likely corresponding reduction in sales) discourages manufacturers from conducting comparative trials. While comparative data exists for a few drugs, no national organization, public or private, synthesizes the existing information so as to provide a decision-making tool for physicians.

This lack of information leads to market failures in which the revenues for new drugs are disproportionate to their value. Drugs with little value may become blockbusters, whereas truly superior drugs which are not promoted by marketing campaigns are under-rewarded. The few comparative studies that have been completed suggest that lack of comparative data leads to substantial inefficient allocation of healthcare spending. In 2002, for instance, the NIH published a long-term study which showed that diuretics, an inexpensive class of drugs that have been in use since the 1950s, were more effective than newer best-selling hypertension drugs that were still on patent (ACE inhibitors and calcium channel blockers).¹⁷⁷ The newer drugs cost 10 to 20 times more than diuretics and are less effective, but thanks to millions spent on marketing campaigns by

¹⁷⁷ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, *The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-converting Enzyme Inhibitor or Calcium Channel Blocker vs. Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)*, 288 JAMA 2891 (2002).

their manufacturers and the absence of comparative data, they became best-sellers.¹⁷⁸ The study's authors believed that the healthcare system could save billions by starting most hypertension patients on diuretics before more expensive alternatives are tried.¹⁷⁹ This is not to say that the newer drugs are not valuable for some patients for whom diuretics are ineffective; but clearly the absence of comparative data created an opportunity for manufacturers to market their newer, patent-protected drugs as the latest and best therapy when, in fact, most patients would have been better off, physically and financially, with the older, less expensive, more effective medication.

Some critics of the current FDA approval process argue that NDA approval of new drugs should be conditioned on demonstrated improvements over existing drugs in head-to-head trials.¹⁸⁰ Such improvements could include greater effectiveness, greater safety, fewer side effects, or substantially greater convenience.¹⁸¹ This argument has some intuitive appeal as it would prevent the mass transfer of patients from off-patent medications to newer, on-patent medications that are, for the average patent, no better. A number of countries whose governments partially or completely subsidize pharmaceutical expenses for their citizens have developed systems along these lines. British Columbia, for example, does not publicly subsidize prescription drug sales until manufacturers provide published scientific evidence of comparative mortality or morbidity benefit.¹⁸² Since coverage decisions are politically-charged, they have been delegated to a university-based group of scientific and medical advisors.¹⁸³ Studies show that when B.C. residents received prescription drugs, they received those from less costly therapeutic classes, chose low-cost drugs within categories, and

¹⁷⁸Melody Peterson, *Diuretics' Value Drowned Out By Trumpeting of Newer Drugs*, NEW YORK TIMES, Dec. 18, 2002, at A32; Editorial, *When Cheaper is Also Better*, NEW YORK TIMES, Dec. 19, 2002, at A38.

¹⁷⁹Merrill Goozner, Editorial, *Prescription for Reform*, Washington Post, Dec. 1, 2003, at A23.

¹⁸⁰*Id.*; Marcia Angell, *The Pharmaceutical Industry – To Whom Is It Accountable?*, 342 JAMA 1902 (2002); see also Editorial, *Comparing Prescription Drugs*, *supra* note 6.

¹⁸¹Relman, *America's Other Drug Problem*, *supra* note 52, at 40.

¹⁸²Special exemptions are made for patients with idiosyncratic needs. Steven Morgan, Ken Bassett, and Barbara Mintzes, *Outcomes-Based Coverage in British Columbia*, HEALTH AFFAIRS, May/Jun. 2004, at 273.

¹⁸³*Id.*, at 270.

purchased generics more often than citizens of other provinces.¹⁸⁴ Similarly, Australia, New Zealand and the United Kingdom have centralized assessment systems which condition subsidization of particular drugs on the manufacturer's demonstration of their comparative effectiveness and/or cost-effectiveness.¹⁸⁵

However, setting the regulatory bar this high has a number of important disadvantages. First, the higher regulatory bar would create disincentives for multiple research efforts within a particular therapeutic class. As discussed in Part II. B., *supra*, DiMasi's research suggests that the prevailing drug development paradigm is one in which a number of firms will pursue drugs with similar mechanisms of action before any drug in the class obtains FDA approval.¹⁸⁶ If improvement relative to already-approved drugs is a condition of approval, this creates a large increase in uncertainty for manufacturers who must not only produce an effective drug, but also produce a drug that is more effective or safe than drugs their competitors are developing, or be the first of the competitors within a therapeutic class to gain FDA approval. This increase in risk would no doubt result in fewer approved drugs in each therapeutic class. This may mean that the best medication for a particular subpopulation, or individual fails the approval process because it is not an improvement for the larger population or because the manufacturer does not choose to invest the resources necessary to identify the subpopulation for which it is most effective. In addition, the effect of fewer drugs in a therapeutic class would reduce competition within therapeutic classes, allowing manufacturers more leeway to charge high prices.¹⁸⁷ In addition, a requirement of comparative trials could add substantially to the cost of trials necessary for FDA approval. If what counts as an approved drug is moving target (as competitors are granted approvals), a firm developing a drug will face unexpected modifications to ongoing clinical trials.¹⁸⁸

Making approval contingent on a showing of increased efficacy might also increase the number of subjects

¹⁸⁴*Id.*, at 274.

¹⁸⁵Steven G. Morgan, Meghan McMahon, Craig Mitton, Elizabeth Roughead, Ray Kirk, Panos Kanavos, and Devidas Menon, *Centralized Drug Review Processes In Australia, Canada, New Zealand, And The United Kingdom*, HEALTH AFFAIRS, Mar./Apr. 2006, at 337.

¹⁸⁶DiMasi, *The Economics of Follow-On Drug Research and Development*, *supra* note 86, at 12-13.

¹⁸⁷Robert A. Bohrer, Letter, *The Pharmaceutical Industry – To Whom Is It Accountable*, 343 NEW ENGLAND J. MED. 1415 (2000).

¹⁸⁸DiMasi, *The Economics of Follow-On Drug Research and Development*, *supra* note 86, at 12-13.

required.¹⁸⁹ On the other hand, industry critics argue that the costs of clinical trials currently reflect the cost of designing trials to benefit the marketing efforts of companies that generate little useful information for physicians, and that current costs may therefore overstate what is necessary to show health benefits.¹⁹⁰ While a showing of comparative improvement sets the bar too high for FDA approval, it should be conditioned on the provision of comparative data showing the drug's performance relative to the most widely used alternative. This standard would not require a showing of increased effectiveness or safety, thus reducing disincentives to developing multiple drugs in a therapeutic class. On the other hand, a requirement of comparative data would make it harder for pharmaceutical companies to market their new drugs as improvements without substantial evidence showing improvement, and thus could be expected to depress revenues from drugs which are not improvements for the average patient. Some disincentive to developing competing drugs for a particular indication would therefore remain.

Alternatively or concurrently, incentives could be designed to encourage voluntary comparative testing. In that scenario, it seems likely that no firm would submit comparative data unless it showed an improvement or unless the FDA regulations included a requirement that manufacturers submit data from all trials sponsored by the manufacturer. If most NDAs included comparative data, the absence of such data could signal to physicians that no improvement over existing drugs is likely. The FDA has some experience with providing incentives for additional research through the pediatric testing provisions of the 1997 Food and Drug Modernization Act ("FDAMA"). FDAMA offered a 6-month extension of marketing exclusivity in return for pediatric testing.¹⁹¹ The FDAMA incentive resulted in only a modest increase in the percentage of drugs tested in children,¹⁹² while providing participating pharmaceutical manufacturers with additional

¹⁸⁹Thomas A. Hayes, Letter, *The Pharmaceutical Industry – To Whom Is It Accountable*, 343 NEW ENGLAND J. MED. 1415 (2000).

¹⁹⁰Goozner, *Prescription for Reform*, *supra* note 179.

¹⁹¹Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 111, 111 Stat. 2296, 2305-09 (codified as amended in 21 U.S.C.).

¹⁹²Lauren H. Breslow, Note, *The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing*, 40 HARVARD J. LEGISLATION 133, 158-59 (2003) (comparing

revenues far in excess of the costs of the pediatric testing.¹⁹³ Scholarship identified several flaws in the pediatric incentive provisions, including failure to address off-patent and off-exclusivity drugs, failure to promote testing in small markets, and limited capacity to ensure labeling and dissemination of information.¹⁹⁴ This experience with pediatric testing suggests that purely voluntary testing would not be enough to promote transformational change in the availability of comparative data. Indeed, less industry response might be expected to a voluntary incentive for comparative testing, since the risk to revenue is probably substantially greater for comparative testing of drugs than for pediatric testing.

The modest impact of providing incentives in the pediatric context on the availability of subpopulation information suggests that comparative testing ought to be a mandatory rather than voluntary part of NDA approval. The purpose of such a requirement would not be to prevent drug approvals for less cost-effective drugs, but to inform physician decision-making and therefore to increase the likelihood that blockbuster profits will not be earned by drugs which do not provide an improvement for a substantial population of patients. In this scenario, the makers of the most effective drugs will be duly rewarded, even in the absence of marketing campaigns.

A system of incentives might be added such that additional testing to identify the subpopulations in which a drug is particularly effective is rewarded, even if the resulting market is quite limited. An increase in the exclusivity period could be triggered by comparative data which shows significant improvements in identifiable populations, such as minorities, women, or people with particular genotypes.¹⁹⁵ Research standards would have to be issued to identify the characteristics of valuable data. For example, incentives should not reward “comparative” studies like the Nexium-Prilosec trial in which a double dose of Nexium was compared to a

Senate Report stating that, in 1997, Congress enacted pediatric testing provisions of FDAMA in response to the fact of only 20% of medications having been tested in children to GAO report that in 2001, 25% of medications had been tested in children).

¹⁹³The *Wall Street Journal* reported the following revenues: Claritin \$ 975 million, Prozac \$ 831 million, Glucophage \$ 648 million, Pepcid \$ 290 million, Vasotec \$ 318 million, and Buspar \$ 284 million. According to a 2001 GAO report, PhRMA estimated trial costs at \$5-\$35 million, while other research organizations estimated far lower costs. *Id.*, at 168 fn301 (2003).

¹⁹⁴*Id.*, at 165.

¹⁹⁵This data would have to be submitted at time of NDA to prevent incentive to stagger studies to extend exclusivity period *ad infinitum*. On the other hand, policy-makers may need to allow some flexibility to prevent delays in initial drug approval.

single dose of Prilosec.

Institutional Considerations – Who Should Provide Comparative Data?

Assuming that a system of mandatory comparative testing and voluntary incentives for testing in subpopulations were instituted, this would raise an issue of which institutions ought to be providing and reviewing the data. One possibility would be to expand on the current NDA process such that the FDA is charged with regulating study design and assessing studies submitted by manufacturers. Public choice theory, however, suggests that an FDA-controlled process would create opportunities for special interest lobbying and agency capture.¹⁹⁶ Furthermore, empirical studies have shown that manufacturer-sponsored comparative studies are overwhelmingly likely to favor the manufacturer's drug.¹⁹⁷ For example, the *Washington Post* reported that in comparative trials of schizophrenia medications Zyprexa and Risperdal, Zyprexa was found to be superior in five of five trials sponsored by its maker, and Risperdal was demonstrated to be superior in three of four trials sponsored by its maker.¹⁹⁸ A broader study of schizophrenia medications found that 90% of published head-to-head trials sponsored by manufacturers show that the sponsor's drug is superior.¹⁹⁹ Possible sources of bias included doses and dose escalation, study entry criteria and study populations, misleading

¹⁹⁶Dan L. Burk and Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1637 (2003).

¹⁹⁷Timothy R. Howe, *Patentability of Pioneering Pharmaceuticals: What's the Use?*, 32 SAN DIEGO L. REV. 819, 819 fn. 2 (citing Joel Lexchin, Lisa A. Bero, Benjamin Djulbegovic, and Otavio Clark, *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, BRITISH MEDICAL JOURNAL, May 31, 2003, at 1-10; and Justin E. Bekelman, Yan Li and Cary P. Gross, *Scope and Impact of Financial Conflicts of Interest in Biomedical Research*, 289 JAMA 454 (2003)).

¹⁹⁸Shankar Vedantam, *Comparison of Schizophrenia Drugs Often Favors Firm Funding Study*, WASHINGTON POST, Apr. 12, 2006, at p. A1, available at <http://www.washingtonpost.com/wp-dyn/content/article/2006/04/11/AR2006041101478.html> (last accessed Apr. 13, 2006).

¹⁹⁹Stephan Heres, M.D., John Davis, M.D., Katja Maino, M.D., Elisabeth Jetzinger, M.D., Werner Kissling, M.D. and Stefan Leucht, M.D., *Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics*, 163 AM. J. PSYCHIATRY 185-194 (2006), available at <http://ajp.psychiatryonline.org/cgi/content/abstract/163/2/185?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&author1=davis&and> (last accessed Apr. 12, 2006).

uses of statistical methods, and reporting of results and wording of findings.²⁰⁰ Large purchasers may also be interested in sponsoring research, though one might suspect that their studies would show a systematic bias towards disfavoring more expensive drugs.

Scholars in the field have advocated for both research and assessment by independent researchers. Healthcare economist Uwe Reinhardt argues that any data provided by manufacturer-funded or insurer-funded studies would not be trusted and recommends allocating government funding for cost-effectiveness studies by independent researchers.²⁰¹ Third party payers could then use this data to develop reimbursement criteria that promote cost-effective utilization by patients and physicians. Similarly, Brigham and Womens' Hospital's chief of Pharmacoepidemiology and Pharmacoeconomics Jerry Avorn, M.D. argues that a government entity probably could not supply objective assessments of effectiveness, since manufacturers have powerful incentives to ensure that agencies do not issue revenue-crippling findings about a new drug's relative lack of efficacy (or even comparable efficacy with less of a track record for safety). Avorn therefore suggests private sector actors be charged with information gathering and dissemination.²⁰²

Mandatory testing by independent researchers would require some form of federal funding. Currently, there is limited federal funding for comparative effectiveness research, and expansion of funding is opposed by the pharmaceutical industry.²⁰³ In academia, some independent research collaboratives produce and synthesize comparative data, but not on the scale needed to make significant changes in physician practice patterns. The Drug Effectiveness Review Project ("DERP") at the Oregon Evidence-Based Practice Center, an academic collaboration that receives some federal funding, is perhaps the best known of these initiatives. It conducts reviews of comparative effectiveness data for major therapeutic classes.²⁰⁴ DERP's reach is limited,

²⁰⁰*Id.*

²⁰¹Uwe E. Reinhardt, *Perspective: An Information Infrastructure for the Pharmaceutical Market*, HEALTH AFFAIRS, Jan./Feb. 2004, at 107-112.

²⁰²JERRY AVORN, POWERFUL MEDICINES, *supra* note 17, at 366-68.

²⁰³Editorial, *Comparing Prescription Drugs*, *supra* note 6.

²⁰⁴<http://www.ohsu.edu/drugeffectiveness/index.htm> (last accessed Mar. 28, 2006).

however, as it does not review all new drugs and it makes no coverage recommendations.²⁰⁵

The necessity for federal funding should be considered in the context of the enormous federal subsidy provided to the pharmaceutical industry by patent protection. In the absence of meaningful data to distinguish between important advances and insignificant advances, the low nonobviousness threshold for pharmaceuticals “signals a decision to provide massive subsidization of the entire industry.”²⁰⁶ Direct federal subsidization of trial costs on the other hand would enable explicit judgments about the value of certain innovations and enable the patent reward to more closely track the actual benefit to society. Well-informed physicians and patients would be able to make decisions about consumption of prescription drugs that more accurately reflects the value of such drugs to patients. Manufacturers will “automatically factor in the preferences of informed consumers and their agents (physicians) when making their decisions to initiate or continue development projects.”²⁰⁷ Informed decision-making, however, presumes that useful information will not be overwhelmed by manufacturer’s marketing campaigns and thus might require simultaneous funding for efforts to improve physician education, training, and continuing education.

III. B. Prevention of Double Patenting

The second major problem created by the interaction of market failure, patent law and the Hatch-Waxman Act is that patents declared invalid for obviousness by the courts, because they fail the Patent Act’s minimal standard for innovation, are nonetheless valuable revenue-generating or protecting tools for their owners.

As discussed in Part I.C., *supra*, even a patent whose validity is likely to be successfully challenged on the

²⁰⁵Morgan, *Centralized Drug Review Processes In Australia, Canada, New Zealand, And The United Kingdom*, *supra* note 185.

²⁰⁶See Michael H. Davis, *Patent Politics*, 56 S.C.L. REV. 337, 369 (2004).

²⁰⁷DiMasi, *The Economics of Follow-On Drug Research and Development*, *supra* note 86, at 13.

merits triggers an automatic stay on generic entry, which results in an extra two and half years of artificially-enhanced revenues for the patent holder. This means that even a very high standard for nonobviousness applied by the courts (as opposed to the PTO) cannot completely prevent this phenomenon. However, there are opportunities to reduce the frequency of issuance of patents that are likely to be invalidated. In order to address this issue, policymakers could change the standard of nonobviousness applied by the PTO during the patent issuance process, make changes to the review process itself, and/or create disincentives to filing applications for weak patents.

III. B. 1. Standards for Nonobviousness and Double Patenting

Changing the standard of nonobviousness applied by the PTO is one possible mechanism for reducing the payoff for incremental innovations. The PTO endeavors to apply the standard of nonobviousness developed by the Supreme Court and Federal Circuit.²⁰⁸ If a drug is obvious as defined by the courts, in light of a previously patented drug, it should, in theory, be impossible to obtain a patent. The courts have developed a doctrine of “double patenting” that prohibits the extension of patent term by subsequently patenting a putatively different drug that is indistinct from a drug claimed in an earlier patent. Double patenting doctrine precludes one person from obtaining more than one patent for the same invention or obvious modifications of the same invention.²⁰⁹ This doctrine has two basic rationales. First, the doctrine prevents patent term extension past the statutory limit of 20 years. The Federal Circuit has stated that the basic concept of double patenting is that an already-patented invention or obvious variants thereof cannot be re-patented, since the second issued patent would result in the extension of patent protection for the first invention beyond the

²⁰⁸UNITED STATES PATENT AND TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE, §2142, (2001, rev. 2005), available at <http://www.uspto.gov/web/offices/pac/mpep/mpep.htm> [hereinafter MPEP].

²⁰⁹DONALD S. CHISUM, CHISUM ON PATENTS, §9.01 (2005).

statutory term.²¹⁰ A second concern is that even multiple patents issued on the same day for the same invention or obvious variants thereof, which do not extend patent term, can be the basis of multiple suits against an alleged infringer.²¹¹ The double patenting doctrine has not been codified in the statute, but the Supreme Court has found it implicit in the statutory language that two valid patents cannot be issued for the same invention to either the same or different parties.²¹² The double patenting inquiry thus would seem to preclude the patenting of many of the types of compounds or methods which give rise to the evergreening phenomenon. For instance, in the case of Prilosec and Nexium, one might anticipate that the patent for the purified isomer Nexium would be invalid for double patenting, if it yields no unexpected results relative to its parent compound.

The test for an obvious modification giving rise to a finding of double patenting is basically the same as the nonobviousness requirement of patentability (though with a few distinct differences).²¹³ Given that the PTO endeavors to follow the obviousness standards defined by the Federal Circuit, this doctrine should bar the issuance of patents that would later be vulnerable to challenges on double patenting grounds. The statutory requirement of nonobviousness states that a patent cannot issue if

the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.²¹⁴

In *Graham v. John Deere Co.*, the Supreme Court articulated the analysis for determining whether an invention is nonobvious as follows:

²¹⁰ *General Foods Corp. v. Studiegesellschaft Kohle mhH*, 972 F.2d 1272, 1279-80 (Fed. Cir. 1992).

²¹¹ Chisum, CHISUM ON PATENTS, §9.02[3], *supra* note 209.

²¹² *Miller v. Eagle Mfg. Co.*, 151 US 186, 197 fn2 (1894). *Miller* is the leading Supreme Court case since it is the only one with a full discussion of the subject. Chisum, CHISUM ON PATENTS, §9.02[6], *supra* note 209.

²¹³ *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 fn. 1 (Fed. Cir. 2003) (First, obviousness compares claimed subject matter to the prior art, whereas double patenting compares claims in an earlier patent to claims in a later patent or application. Second, obviousness analysis requires an inquiry into a motivation to modify the prior art; double patenting analysis does not. Third, obviousness analysis requires an inquiry into objective indicia of nonobviousness, but double patenting analysis does not.) *Also see generally*, Chisum, CHISUM ON PATENTS, §9.01[1], 9.03[3][c], *supra* note 209.

...the scope and content of the prior art are to be determined; differences between prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. This requirement is meant to distinguish inventions that are worthy of a patent from those that are not on the basis of their degree of technical advance over prior art. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc. might be utilized... [a]s indicia of obviousness or nonobviousness...²¹⁵

Thus, the nonobviousness requirement calls for an inquiry into the degree to which an invention is a significant technical advance over already available technology in the relevant field. This suggests that one possible policy solution for the concerns raised by evergreening might be to raise the standard for nonobviousness applied by the PTO.²¹⁶

The obviousness standard is set at a particularly low level for chemical inventions. In *In re Dillon*, the Federal Circuit held that structural similarity where the prior art gives motivation to create the claimed compound creates a presumption of obviousness, but the presumption may be rebutted by proof of unexpectedly improved properties or properties that the prior art does not have.²¹⁷ The court in *In re Papesch*, had stated that nonobviousness is not established conclusively if the unexpected property is a “mere difference in degree” of the same desired property relied on for patentability in the new compound.²¹⁸ Later decisions, however, extended the concept of “unexpected properties” to embrace “significant differences in degree of the same property amounting to marked superiority.”²¹⁹ In *In re Soni*, the Federal Court appeared to lower

²¹⁶The standard of nonobviousness has been widely criticized as being too low as a general matter across all industries. See e.g. John H. Barton, *Nonobviousness*, 43 IDEA 475 (2003). Efforts are currently under way to increase the standard of nonobviousness by eliminating the Federal Circuit’s requirement of a showing of a “motivation to combine” to establish obviousness. Where the invention comprises a combination of teachings in prior art, the courts will inquire into whether the prior art suggests, either implicitly or explicitly, a “motivation to combine” in order to determine whether the invention is obvious as a matter of law. This has led to concern that patents are inappropriately granted to otherwise obvious inventions, because “[p]atent examiners and after-grant challengers will often be unable to find a specific ‘suggestion, teaching, or motivation’ for a particular combination of existing elements, even if that combination is not innovative. In many cases, it would be so natural for a person of ordinary skill in the art to use two existing elements together in appropriate circumstances that no one would think of articulating explicitly the kind of ‘suggestion, teaching, or motivation’ that the Federal Circuit requires.” *KSR Intl’l v. Teleflex Inc.*, No. 04-1152, Brief of Twenty Four Intellectual Property Law Professors as *Amicus Curiae* in Support of Petitioner, at 11. Also see *KSR Intl’l v. Teleflex Inc.*, No. 04-1152, Petition for *Writ of Certiorari*, April 6, 2005.

²¹⁷919 F.2d 688, 692-93 (Fed. Cir. 1990). Also see Chisum, CHISUM ON PATENTS, §5.04[6][d] & [e], *supra* note 209.

²¹⁸*In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963).

²¹⁹Chisum, CHISUM ON PATENTS, §5.04[6][e], *supra* note 209 (citing *In re Hoch*, 428 F.2d 1341, 1344 n.5 (C.C.P.A. 1970)).

the bar further when it stated that while “mere improvement in properties does not always suffice to show unexpected results... when an applicant demonstrates substantially improved results... *and states that the results were unexpected*, this should suffice to establish unexpected results in the absence of evidence to the contrary” (emphasis added).²²⁰ Although the court stated that unexpected results must be established by objective evidence, not mere argument or conclusory statements (and has been cited for this proposition by subsequent cases), the court appeared to have accepted a mere statement of unexpectedness by the manufacturer as a sufficient showing to rebut the *prima facie* case for nonobviousness.²²¹

Ortho-McNeil Pharmaceuticals Inc.v. Mylan Labs., Inc. provides a recent case study of the application of the nonobviousness test in the context of stereoisomers (categorized in Part II , *supra*, as “obvious to try” and low or substantial benefit).²²² The brand name manufacturer, Ortho-McNeil Pharmaceuticals first patented a racemic mixture of its antibiotic, and later patented the purified active stereoisomer. Generic manufacturer Mylan challenged the patent for the purified stereoisomer as invalid for obviousness. The court concluded that the challenger did not establish a *prima facie* case of obviousness. While conceding that the prior art in 1985 suggested that one of the stereoisomers would be more potent than the racemate and that there was sufficient guidance in the prior art to produce a purified stereoisomer, the court reasoned that a skilled artisan would not have reasonably expected the purified stereoisomer to exhibit its unique combination of properties. The court emphasized that while it was well-established in the prior art that one of the purified stereoisomers in a racemate is usually more potent than the racemate, potency usually varies directly with toxicity, so a purified stereoisomer that is both more pure and less toxic than the racemate was not expected.²²³ In addition, the court noted that the prior art suggested a range of possible potencies

²²⁰*In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) (emphasis added).

²²¹*Id.*, at 750.

²²²*Ortho-McNeil Pharmaceuticals Inc.v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713 (N.D.W.V. 2004)

²²³*Id.*, at 753-755.

but did not teach that the purified stereoisomer is consistently twice as potent as the racemate, as was true for the compound at issue.²²⁴ The court concluded that to prove obviousness, the challenger must show that, as of the date of invention, “the prior art would not only motivate a person of ordinary skill in the art to make [the compound], but also reasonably suggest that the compound would exhibit *its unique combination of properties*.”²²⁵ This seems like a particularly low standard for nonobviousness given that it is well-established in the pharmaceutical field that one of the stereoisomers in a racemate is usually responsible for the therapeutic effect of the drug.

Economic analysis of the pattern of innovation in the pharmaceutical industry is necessary to determine whether the low standard of nonobviousness currently applied by the Federal Circuit is set at the correct level to maximize incentives to invention. Robert Merges developed the classic economic analysis of the nonobviousness standard, which describes it as a function of the uncertainty facing the inventor.²²⁶ Merges analyzes invention as a two-step process: first, the inventor makes some initial assessment of potential returns from an invention prior to beginning experimentation. Then, the inventor decides whether to develop the invention or abandon it.²²⁷ At each stage, the inventor makes a decision based on the expected value of the project. By increasing the expected payoff, the patent increases the expected value of the project and may in some cases turn a project with an otherwise negative expected value into a project with a positive expected value. Through the use of a simple mathematical model, Merges argues that the availability of a patent has an even greater effect on the decision about whether to develop an invention into a commercial product than it does on the decision about whether to pursue initial experimentation.²²⁸ He then argues that the standard of nonobviousness should “reward[]one who successfully invents when the *uncertainty facing her prior to the*

²²⁴ *Id.*, at 754.

²²⁵ *Id.*, at 749 (emphasis added).

²²⁶ Robert P. Merges, *Uncertainty and the Standard of Patentability*, 7 HIGH TECH. L. J. 1, 20 (1993).

²²⁷ *Id.*, at 21.

²²⁸ *Id.*, at 33.

invention makes it more likely than not that the invention won't succeed"²²⁹ If the uncertainty facing the inventor is low, such that the expected value of the project is positive, then there is little social gain from granting a patent, since the less risky project would be undertaken without the additional social cost of monopoly prices associated with patent protection. There may be additional social costs associated with granting patents to low-risk projects if firms redirect their research away from high-risk invention and toward less risky projects."²³⁰ It follows from Merges' proposed standard that the more uncertain the development of a successful product is, the more patent protection is needed to offset the low expected value of a high-risk project, and correspondingly, the lower the nonobviousness standard should be. He notes that one objection to this standard is that this will create incentives for more high-risk research, which will displace low-risk research. Merges responds that this is likely true, but if the social rate of return is higher from high-risk endeavors, then this is a good result.²³¹ (It is important to note though that his proposed standard does not rest on the veracity of this inference.)

Merges carves out an exception to the direct relationship between uncertainty and the nonobviousness standard for cases in which there is a high certainty of success, but which involve very high experimentation costs. Merges argues that patents should be easier to obtain for the results of high-cost research projects than they are for low-cost projects.²³² Higher costs decrease the expected value of a research project. In order to offset the decrease in expected value due to high costs, the firm investing in the project will consider the payoff, which is a function of the degree to which it can appropriate the benefits of the invention.²³³ A lower standard for patentability, which increases the expected value of the project, is thus necessary to create an incentive for high-cost projects.²³⁴

²²⁹*Id.*, at 20.

²³⁰Robert M. Hunt, NONOBVIOUSNESS AND THE INCENTIVE TO INNOVATE: AN ECONOMIC ANALYSIS OF INTELLECTUAL PROPERTY REFORM (Fed. Reserve Bank of Philadelphia Research Dept. Working Paper No. 99-3, Mar. 1999) <http://www.phil.frb.org/files/wps/1999/wp99-3.pdf> (last visited Feb. 9, 2006), at 11.

²³¹Merges, *Uncertainty and the Standard of Patentability*, *supra* note 226, at 20.

²³²*Id.*, at 57.

²³³*Id.*, at 62.

²³⁴*Id.*

Pharmaceutical invention appears to be a paradigmatic case of a high-risk, high-cost invention. For virtually all break-through drugs and many follow-on drugs, development of a commercial product is high-risk due to the complexity of living systems, and high-cost because of demanding FDA testing requirements. Thus, if Merges' analysis is applied to the pharmaceutical industry, it would suggest that a low standard of obviousness is appropriate. The current low standard in Fed Cir., discussed in above, is consistent with this analysis.

Other drugs, however, can be fairly characterized as low-risk, such as a purified metabolite of a drug that is known to be safe and effective. The question begged is whether a low standard of nonobviousness, applied at the industry level, would then allow patent protection for drugs that would have been developed in the absence of patent protection. The likely answer is no, given the special circumstances faced by the pharmaceutical industry. A new drug, however probable it is to succeed, nonetheless must meet FDA testing requirements before it can be commercialized. This means that drug companies face substantial costs to develop even products that are virtually certain to pass the requirements for commercialization. The expected value of such projects, however, would significantly decline in the absence of patent protection because generic competitors face only the less costly ANDA process in order to copy and commercialize the inventor's product. We might then expect some number of low-risk drugs never to be developed if a higher standard for nonobviousness were applied to them. Thus, if the development of high-value, low-uncertainty drugs is desirable, the application of Merges' theory (particularly his analysis of high-cost invention) suggests that a low standard of nonobviousness is appropriate.

An economic model developed by Hunt also suggests that a low obviousness standard is appropriate for the pharmaceutical industry. Hunt divides the incentive effect of the nonobviousness standard into a "static" effect and a "dynamic" effect.²³⁵ He argues that most economic analysis of nonobviousness focuses on the "static" effect, which as Merges describes, means that increasing the standard decreases the probability of a

²³⁵Hunt, NONOBVIOUSNESS AND THE INCENTIVE TO INNOVATE, *supra* note 230, at 4.

patent and therefore decreases the expected value of innovation. The “dynamic” effect of the nonobviousness standard, by contrast, is that as the standard increases, the value of the patent increases so the expected value of the innovation increases. Expected value increases under a strong nonobviousness requirement because if the standard is high

... only a small proportion of future discoveries is protected. Today’s patent holder can copy most of the emerging discoveries. Competing proprietary technologies take longer to accumulate so the patent holder’s profits are larger and last longer. Thus, holding the rate of innovation constant, the economic life of patents is increasing [with] the standard of nonobviousness. This suggests that the value of patents is increasing [with] the strictness of the nonobviousness requirement.²³⁶

Which of these two effects predominates, depends on a number of variables, especially the pace of innovation in the industry. Hunt contends that Merges’ analysis, which focuses on the static effect, is least appropriate in rapidly innovating industries and most appropriate in industries in which products are introduced at a slow rate:²³⁷

As the nonobviousness requirement is made more strict, firms encounter the following trade-off. On the one hand, a firm that makes a marginal discovery fails to obtain a patent and continues as a challenger in the next race. It loses the associated profit and the cost of R&D spending it would have avoided for the length of the next race.... When patentable discoveries are infrequent, these losses are relatively large. But when patentable discoveries occur frequently, the value of these losses is smaller. On the other hand, a stricter nonobviousness requirement raises the average flow profit of patentable discoveries. The associated gain [increases with] the frequency of patentable discoveries. The net effect is a weighted average of these cash flow gains and losses, where the weights are determined by the industrywide arrival rate of patentable discoveries.²³⁸

As an empirical matter, it is not clear whether the static or dynamic effect of the standard of nonobviousness predominates in the pharmaceutical industry. However, given the inherent complexity of biological systems and the FDA testing required for commercialization, the pharmaceutical industry most likely fits the model of a slow innovator. So, even if Hunt’s model more accurately depicts the effect of the standard of nonobviousness on incentives for innovation, it would still likely support a low standard of obviousness.

²³⁷ *Id.*, at 4.

Consistent with this analysis, Dan Burke and Mark Lemley find that the application of Merges' theory to that field would make a low standard of nonobviousness sensible in the biotechnology and small molecule pharmaceutical fields.²³⁹

However, rather than endorsing a low standard of nonobviousness, Burk and Lemley propose that investment in fields which development is high-cost and high-risk can be better promoted by broadening patent scope.²⁴⁰

A broader patent increases the expected value of an invention by increasing the value of a patent once it is granted (by excluding more competition), rather than by increasing the probability of getting a patent.²⁴¹

An increased probability of getting a patent, they contend, is an inferior means of fostering innovation in high-cost, high-risk industries, because it creates an additional incentive only for projects which are relatively low-risk and low-uncertainty. An increased probability of getting a patent does nothing to increase the expected value of a high-risk project that would pass even a high nonobviousness threshold, but a broader patent scope would increase the payoff to such inventions.

One way to analyze Burke and Lemley's and Merges' theories in the context of the pharmaceutical industry is to ask what effect they would have on incentives in light of the current regulatory structure, particularly the Hatch-Waxman Act. The answers will likely vary depending on whether markets for drugs are functioning well (in the sense that the revenues from drugs reflected their value to those who buy them). This discussion will assume that some set of reforms, such as the requirement of comparative testing discussed in Part III.

²³⁹Burk, *Policy Levers in Patent Law*, *supra* note 196, at 1677-78.

²⁴⁰*Id.*, at 1676-77, 1681-1682. Such broadening could occur by reducing the disclosure requirement or by strengthening the doctrine of equivalents. The disclosure requirement of the Patent Act establishes that the patent applicant must provide a "written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. §112 (2006). The analysis which the PTO and the courts use to determine whether the products claimed by a patent are enabled within the meaning of the statute can determine whether the patent has a broad or narrow scope. See Robert P. Merges and Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUMB. L. REV. 839, 845-49 (1990). Similarly, application of the doctrine of equivalents may be used to broaden or narrow patent scope. The doctrine is applied during the claim construction process of infringement suits to allow some range of products, which do not literally infringe the claims of the patent, to be considered as encompassed by the claims. Application of this doctrine, therefore, broadens the reach of patent claims. See *id.*, at 852-860.

²⁴¹Burk, *Policy Levers in Patent Law*, *supra* note 196, at 1681.

A., *supra*, are in place, so that physician and patient decision-making reflects accurate information about the benefits of the drugs available to them. Thus, this discussion will assume that patients will not choose drugs that are more expensive, but offer them no additional benefit, over a competing drug.

As discussed in Part II. C., *infra*, the patent system should be designed to promote the development of drugs with the most substantial benefits to patients. This degree of benefit will be based both on inherent properties of the drug and the work that the manufacturer has done to identify patients likely to benefit most from it. If markets are working properly, drugs with expected insignificant or low social value, will probably not be developed regardless of the patent scope or patentability standards, since expected returns to the manufacturer will not overcome the costs of required FDA testing. This category might sweep in some inventions which would substantially benefit some patients, but where those populations of patients are small and/or unidentified.²⁴²

Arguably, a high obviousness standard in combination with broader patent scope would provide greater incentives to develop innovative drugs that have the greatest social value. Under the current standards, these drugs meet the nonobviousness standard, so the expected value of development already reflects monopoly prices. However, it is not clear that the incentives to innovate are strong enough. Pharmaceutical manufacturers can plausibly argue that even with patent term restoration and market exclusivity, the expected rewards must include revenues not only from the original new drug, but also revenues from incremental modifications to these drugs in order to achieve a positive expected value in light of the cost of required testing and enormous uncertainty. An increase in the nonobviousness standard accompanied by an increase in patent scope, however, would likely achieve greater returns for the most innovative drugs. Broader patent

²⁴²One important objection to this approach is that drugs that are no better for the average patient may nonetheless be better for particular individual patients, so society is better off if we have many options for treating a disease even if there is no reliable data about for whom a new drug is any better than its predecessors. Drugs like this present a problem similar to drugs for whom populations are too small to make the expected value of a development project positive (“orphan drugs”). As with orphan drugs, they may require a separate regulatory solution, possibly via direct subsidization, about which explicit political judgments can be made.

scope would increase the expected value of the drug, by encompassing some incremental improvements that currently require a second patent in order to be protected. If it is these drugs that public policy should most strongly promote, then a grant of broader patent scope makes sense.

One objection to broad patents is that they deter innovation by preventing other inventors from competing with the patent holder in a larger range of products than a narrow patent would. Merges and Nelson argue that broader patents do not always increase incentives to invent. Rather, they may do so for some pioneers, but then diminish the incentives for later inventors who seek to improve a product.²⁴³ In contrast, Edmund Kitch, who developed the “prospect theory” of patent law, argued that a broad patent promotes improvements by giving the pioneer inventor an incentive to make investments in improving the subject of his patent without the risk that the investment would result in “unpatentable information appropriable by competitors.”²⁴⁴ Furthermore, he argued that a broad patent can increase the efficiency of investment in improvements, since a broad patent right puts the pioneer patent holder in the position of being able to coordinate the search for improvements (thus avoiding duplicative research efforts) by developing the product itself or licensing. In the context of small improvements to a drug, for example, by new delivery methods or doses, it makes intuitive sense that the original patent holder would be best situated to make such improvements. Given the uniquely high costs of development, the original inventor may have the best information on which to base improvements.²⁴⁵ In sum, this analysis suggests that the best way to provide incentives for break-through innovation is to raise the bar for nonobviousness and expand patent scope.

We might then consider how a higher standard of nonobviousness and broader patent scope would affect drugs with substantial or great social value that meet the current nonobviousness standard, but would not meet a substantially raised standard. Two outcomes seem possible. One is that these inventions would not

²⁴³Merges, *On the Complex Economics of Patent Scope*, *supra* note 240, at 916.

²⁴⁴Edmund W. Kitch, *The Nature and Function of the Patent System*, in FOUNDATIONS OF INTELLECTUAL PROPERTY LAW, 140, 146 (Robert P. Merges and Jane C. Ginsburg, eds., 2004).

²⁴⁵See generally, Burk, *Policy Levers in Patent Law*, *supra* note 196, at 1686.

be patentable and therefore would remain undeveloped, since monopoly prices would not be available to offset the costs of required FDA testing. On the other hand, this likely outcome would encourage inventors to include claims in the original patent for likely modifications of the drug (e.g., purified stereoisomers and metabolites). This would increase the amount of research that would have to precede patenting, but a relaxed enablement requirement would make the required effort less burdensome. This might have the beneficial effect of encouraging improvements to be developed sooner rather than only as the original patent was nearing expiration.

The current standards of patentability do not promote drugs with substantial or great social value that do not meet the current standard for nonobviousness. Although in theory inventive efforts that produce an obvious result require no incentive other than that which the market provides, in the context of costly testing requirements, even the availability of a substantial consumer base may not be enough to result in a positive expected value. A higher standard of nonobviousness increases the number of drugs which fall into this category.

Thus, neither approach seems ideal. On the one hand, a higher standard of nonobviousness may mean that some less innovative, but high-value drugs will not be developed, and the degree to which increased patent scope can offset this effect is uncertain; on the other hand, a higher standard in conjunction with broad patent scope will increase the expected value of innovative, high-value drugs and provide greater incentives for their development. The existence of the potential for using patents on small improvements as a means of triggering a stay on generic competition under Hatch-Waxman, however, might counsel us to place more weight on the option that provides the least opportunity for evergreening practices described in Part I. D. 2, *supra*. Certainly, the grant of fewer patents would mitigate this issue by reducing the likelihood that patents would issue for small modifications to an existing drug. In the absence of such patents, the manufacturer's economic hold on a drug would more likely expire at the time that the original patent expires.

Given substantial uncertainty about the effect of changing the standard of nonobviousness, however, other policy solutions to the problem of optimally promoting innovation and preventing double patenting are more clearly beneficial, until substantially more detailed economic modeling of the effects of patentability and patent scope on the industry become available.

III. B. 2. Reducing the Payoff from Invalid Patents / Prevention of Double Patenting

Another question that seems to arise from the proliferation of patents on trivial improvements, particularly those that are over-turned by the courts, is why such improvements are not barred by the PTO's examination of the patent application. Even if the standard of obviousness applied by the courts is low, patents should ideally not issue if they do not meet that standard. The unique and substantial social costs associated with erroneously-issued pharmaceutical patents suggests that reforms to the PTO's patent application review process are particularly urgent in this context, and that penalties for double patenting should be considered. Much concern has been expressed in recent years regarding the poor quality of issued patents. In an ideal world, the PTO would never issue a patent that could not meet the Federal Circuit's standards. As a practical matter, however, the PTO operates with limited resources to review hundreds of thousands of patent applications per year, and some error rate is inevitable. Currently, there is evidence that this error rate is unacceptably high. Although the Federal Circuit has been described as "pro-patent" and even captured by business interests, in cases in which patent validity is challenged on appeal, it nonetheless overturns or affirms the overturning of patent claims for invalidity in 46% of the cases that reach it.²⁴⁶ Self-selection bias

²⁴⁶See Paul M. Baisier & David G. Epstein, *Resolving Still Unresolved Issues of Bankruptcy Law: A Fence or an Ambulance*, 69 AM. BANKR. L.J. 525, 539 (1995) (Federal Circuit capture); Steven Cherenky, *A Penny for Their Thoughts: Employee-Inventors, Preinvention Assignment Agreements, Property, and Personhood*, 81 CAL. L. REV. 595, 614 n.86 (1993) (describing the Federal Circuit as pro-patent); FEDERAL TRADE COMMISSION, TO PROMOTE INNOVATION, *supra* note 92, Chapter 5, at 6.

likely causes challenges to patent validity to be appealed only where patents are particularly questionable and thus the 46% rate likely overstates the overall PTO error rate. However, in the pharmaceutical field where the Hatch-Waxman provisions create financial rewards to patent owners for patents issued in error, one might expect erroneously-issued patents to be particularly numerous.

The patent application process in the PTO is commonly described as “cursory,” suggesting a tendency to err on the side of issuance.²⁴⁷ A study by the National Academies of Science (“NAS”) reported that the number of patent applications doubled in the 1990s, but the number of examiners available to review them did not keep pace.²⁴⁸ Estimates of the current average total time spent by an examiner on a patent prosecution (including time to read and understand the application, evaluate the application, and communicate with the applicant) range from 8 to 25 hours.²⁴⁹ The examiner thus has limited time for evaluation, and given that the applicant is not required to search the prior art for relevant material and provide it to the examiner, the examiner may not uncover all of it.²⁵⁰ Some error rate in patent issuance is thus to be expected: it would be unrealistic to think that review of a patent by the PTO would be as searching as what occurs in patent litigation. However, the high approval rates give cause for concern. In his statement to the FTC, Cecil Quillen contended that when the PTO’s approval rate was adjusted for the effects of continuation applications and continuations in part, it was 98% in 2000.²⁵¹ In contrast, the rates in Europe and Japan were 67% and 64%, respectively.²⁵² One observer concluded, “[p]atent office statistics themselves establish that almost any patent lawyer can probably get [a ham sandwich] patented.”²⁵³

²⁴⁷See e.g., Davis, *Patent Politics*, *supra* note 206, at 370.

²⁴⁸Stephen A. Merrill, Richard C. Levin, and Mark B. Myers, Editors, Committee on Intellectual Property Rights in the Knowledge-Based Economy, National Research Council, National Academies of Science, *A PATENT SYSTEM FOR THE 21ST CENTURY*, 2004, at 41, available at <http://www.nap.edu/catalog/10976.html> (last visited Apr. 14, 2005).

²⁴⁹FEDERAL TRADE COMMISSION, *TO PROMOTE INNOVATION*, *supra* note 92, Chapter 5, at 5.

²⁵⁰The “duty of candor” requires that the applicant reveal prior art of which he is aware to the PTO, but does not require him to search for prior art.

²⁵¹The PTO’s Deputy Commissioner for Patent Examination Policy Stephan Kunin disputed this estimate. A later article by PTO legal advisor Robert Clarke put the number at 71-80%.

²⁵²FEDERAL TRADE COMMISSION, *TO PROMOTE INNOVATION*, *supra* note 92, Chapter 5, at 6.

²⁵³Davis, *Patent Politics*, *supra* note 206, at 370, fn131.

While acknowledging the substantial PTO error rate, Mark Lemley has argued that the costs of improving PTO review would outweigh the litigation costs that would be averted by more PTO review:

Because so few patents are ever asserted against a competitor, it is much cheaper for society to make detailed validity determinations in those few [litigated] cases than to invest additional resources examining patents that will never be heard from again. In short, the PTO doesn't do a very detailed job of examining patents, but we probably don't want it to.²⁵⁴

Lemley concludes that the PTO's failure to carefully examine patent applications is a form of "rational ignorance."²⁵⁵ Joseph Farrell and Robert Merges have challenged this assertion, arguing that the incentives inherent in patent litigation, such as severe penalties for unsuccessful challenges to questionable patents relative to a royalty that would otherwise be paid, result in too few challenges being brought and thus allow patent holders to extract rewards from their patents that are disproportionate to their patents' likely strength.²⁵⁶ They therefore argue for reforms to improve the PTO review process. Even if Lemley's analysis more closely reflects the general reality of patent litigation, however, it does not factor in the additional costs of litigation associated with the Hatch-Waxman Act. The Hatch-Waxman Act most likely both increases the number of lawsuits, and increases the social cost of an invalid patent via the thirty-month stay provision. Pharmaceutical patents, therefore, include some subset of patents for which social costs are particularly high, and thus additional PTO review could be economically justified.

In order to reduce the issuance of patents that are invalid for double patenting, more information is needed regarding the sources of error. Lemley suggests that much of the error rate is probably due to failure to identify prior art.²⁵⁷ This, however, is likely a less important source of error in double patenting cases, since the relevant prior art will consist in large part of the applicant's prior patents, which the applicant's duty of

²⁵⁵ *Id.*, at 1511.

²⁵⁶ Joseph Farrell and Robert P. Merges, *Symposium: Ideas into Action: Implementing Reform of the Patent System: Incentives to Challenge and Defend Patents: Why Litigation Won't Reliably Fix Patent Office Errors and Why Administrative Patent Review Might Help*, 19 BERKELEY TECH. L. J. 943, 968-69 (2004).

²⁵⁷ Lemley, *Rational Ignorance at the Patent Office*, *supra* note 254, at 1500.

candor requires him to present in his application.

One more likely source of error is the particular difficulty of applying nonobviousness standard. The nonobviousness standard is likely difficult to apply because it takes the form of a hypothetical thought-experiment in which the examiner is asked to determine what “would have been obvious” to a person of ordinary skill in the art.²⁵⁸ The Federal Circuit has likened the test to the “reasonable man” in tort law:

With the involved facts determined, the decision-maker confronts a ghost, i.e. “a person having ordinary skill in the art,” not unlike the “reasonable man” and other ghosts in the law. To reach a proper conclusion under 102, the decisionmaker must step backward in time and into the shoes worn by that “person” when the invention was unknown and just before it was made...²⁵⁹

Michael Davis argues that the analysis required is so indeterminate and flexible that it “gives license to the courts to roam freely from the facts of a case” and apply their own policy judgments to the case before them.²⁶⁰ To the extent this is the case, it is not surprising that the PTO makes less than perfect predictions about the likely application of the standard by the Federal Circuit.

If Federal Circuit results are somewhat predictable, however, the logical response to the difficulty of applying the nonobviousness standard would be to increase the average expenditure on examinations, so as to allot more time to each examination. Rather than assuming that all patents require a similar amount of examination time, policymakers could take into account the incentives created by the Hatch-Waxman Act and allot more examination resources in particular to pharmaceutical patent applications most likely to be later found invalid for double patenting. These might include all modifications or uses of compounds for which a patent is already in existence.

Another possibility would be to reverse the burden of proof such that applicants for patents must show

²⁵⁸35 USC §103(a) (2006).

²⁶⁰Davis, *Patent Politics*, *supra* note 206, at 1356-57.

nonobviousness. Currently, the USPTO Manual of Patent Examining Procedure states that during prosecution the patent examiner has the burden of showing a *prima facie* case for obviousness-type double patenting by applying *Graham v. Deere* factors.²⁶¹ This means that applicant need not make a showing of nonobviousness until the examiner has presented a case for rejection due to obviousness.²⁶² The difficulty of determining whether the standard has been met, therefore works in favor of the applicant.²⁶³ This is especially troubling if the PTO is to some degree subject to “capture” by applicants and therefore disinclined to challenge applicants.²⁶⁴ Although the benefits of reversal of the burden of proof are plainest for pharmaceutical double patenting, the FTC has argued that the burden of proof is problematic for all patents, particularly given the *ex parte* nature of the proceedings.²⁶⁵

Reforms of the PTO examination process, however, may not be sufficient to address the problem of double patenting if the PTO is, as some observers have argued, subject to regulatory capture.²⁶⁶ Under this theory, the PTO has come to see itself as an agent of patent applicants, rather than a servant of the public interest. It may therefore be biased towards issuing patents, even if it has sufficient time and resources to deny some that will (or ought to) later be struck down by the courts. If this is the case, some sort of disincentive to applying for a weak patent may be needed. One possibility would be to impose penalties on patent holders whose patents are found invalid. In the context of paragraph IV challenges, this penalty could be calibrated to reflect the revenues generated by the patent during the thirty-month stay on generic competition awarded by the Hatch-Waxman provisions.

Robert Merges has analyzed the possibility of penalties for invalid patents by analogizing the costs of torts

²⁶¹Emily A. Evans and Jill A. Jacobson, *Double Patenting Recapitulated*, 87 J. PATENT & TRADEMARK OFFC. SOC'Y 625, 630 (2005) (citing MPEP §804.II.B.1, *supra* note 208).

²⁶²MPEP §2142, *supra* note 208; *also see* FEDERAL TRADE COMMISSION, TO PROMOTE INNOVATION, *supra* note 92, Chapter 5, at 8.

²⁶³*Id.*

²⁶⁴Carl Shapiro, *Symposium: Ideas into Action: Implementing Reform of the Patent System: Patent System Reform: Economic Analysis and Critique*, 19 BERKELEY TECH. L. J. 1017, 1021-22 (2004).

²⁶⁵FEDERAL TRADE COMMISSION, TO PROMOTE INNOVATION, *supra* note 92, Chapter 5, at 8-10.

²⁶⁶Shapiro, *Symposium: Ideas into Action: Implementing Reform of the Patent System: Patent System Reform: Economic Analysis and Critique*, *supra* note 264, at 1038.

to the costs of invalid patents.²⁶⁷ He argues that the PTO is best positioned to bear the cost of preventing invalid patent for several reasons (i.e. the PTO is the least cost avoider). First, prior art that may later invalidate a patent may be unavailable to the patent applicant at the time of filing. There may be economies of scale in allocating the responsibility for prior art searched to the PTO, and it is desirable to shift some of the costs of prior art searches from small inventor to the PTO.²⁶⁸ The difficulty of conducting a thorough search of the prior art might deter some valuable inventive activity. As discussed above, however, this is less likely to be a serious concern in cases of double patenting wherein the most critical prior art consists of the patentee's own applications. (It might be more problematic in the context of patents challenged for obviousness rather than obviousness-type double patenting, although most paragraph IV challenges tend to involve improvements on the patent holder's own inventions.) Second, Merges argues that there is value in a system which prevents issuance of weak patents rather than deterring them with post-litigation remedies, because the high cost of litigation will deter some meritorious challenges.²⁶⁹ Again, this is less concerning in the context of pharmaceutical double patenting, since Hatch-Waxman provides effective incentives to generics manufacturers to challenge invalid patents. It therefore seems that paragraph IV litigation is more amenable than most forms of patent litigation to retroactive remedies for the appropriation of royalties from the public by means of invalid patents.

In summary, in an era in which Americans are increasingly concerned about the affordability of life-saving medications, the efficient allocation of healthcare resources should be a priority for healthcare regulators. The disconnect between the revenues earned from patented pharmaceutical inventions and their likely social value suggests that current patent and regulatory law is not well-calibrated to reward and encourage the

²⁶⁷Robert P. Merges, *As Many as Six Impossible Patents Before Breakfast: Property Rights for Business Concepts and Patent System Reform*, 14 BERKELEY TECH. L. J. 577, 599-600 (1999).

²⁶⁸*Id.*, at 599-600.

²⁶⁹*Id.*, at 600.

most valuable types of innovation. Pervasive market failures combine with the current regulatory structure to create a set of perverse investment incentives for pharmaceutical manufacturers by over-rewarding some inventions relative to their value and under-rewarding others. In order to address this set of problems, policy-makers should consider 1) requiring comparative data in order to qualify for FDA approval, 2) providing incentives for voluntary testing of subpopulations, 3) increasing the standard of nonobviousness in conjunction with broadening patent scope, 4) funding more searching review of patent applications by the PTO and / or reversing the burden of proof in the patent application process for new formulations of known compounds, and 5) instituting post-litigation remedies for patents found invalid in paragraph IV challenges. While these possibilities by no means exhaust all the policies that could be brought to bear on the issue of promoting progress in pharmaceutical research and development, they are illustrative of ways in which the rewards arising from patent protection and market exclusivity can be designed to more accurately reflect the social value of particular innovations.