Excavating Treasure from the Amber of the Prior Art: Why the Public Benefit Doctrine is Ill-suited to the Pharmaceutical Sciences

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Abstract

This paper explores incongruities between patents and regulation as applied to the pharmaceutical industry in the United States. Research, development and marketing of a new pharmaceutical agent generally requires large, high-risk investments. The time and expense of conducting clinical trials to obtain pre-market approval from the Food and Drug Administration provides an additional barrier to entry. The patent system stimulates such investment by providing a legal barrier to appropriation of these investments by free-riders and increasing the likelihood of capital return on these investments. These two barriers are intertwined. For the most part, firms only attempt to clear the regulatory barrier when patent protection is certain. As a result of the uniquely challenging economic situation presented by the regulatory barrier, a common line of reasoning in patent policy and jurisprudence, that inventions which are barred from patenting benefit the public, is flawed. To the contrary, the patent/regulatory system forever traps pharmaceutical inventions, once placed in the public domain. Pharmaceutical companies cannot afford to invest the resources needed to clear the regulatory barrier if the investment is quickly appropriated by a free-riding manufacturer. Various implications of, and solutions to, this policy artifact are explored.

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I. Introduction to pharmaceutical industry and economic predicates

A. The history and economics of the pharmaceutical industry

Pharmaceutical researchers have contributed greatly to improving the human condition over the last century. As the "low hanging fruit" has been harvested, the pace of progress toward further improving the length and quality of human lives has progressively decreased. Early breakthroughs are exemplified by Bayer's commercialization of acetylsalicylic acid, a relatively easily produced form of a simple natural product (willow bark extract) that had been used since ancient times.[1] As the industry has developed and matured, the cost of bringing additional molecules to market has increased dramatically. Although estimates vary, taking into account failed development programs and product recalls, the cost of developing a new small-molecule drug is now measured in the hundreds of millions of dollars (as high as $1.5 billion, by some estimates) and takes on the order of 14 years.[2,3] There at least two sources for the increased development costs. First, because of previous advances, the difficulty of producing a drug that is non-inferior, or more challengingly, superior in terms of safety and efficacy to those already marketed becomes more difficult over time. Second, the Food and Drug Administration (FDA) presents a difficult barrier to approval. In making its determinations, the agency considers the safety of the drug, the proven benefits of the drug, and performs a cost-benefit analysis. In this way, the two reasons are intertwined; a

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[1] See Wikipedia, "Aspirin", http://en.wikipedia.org/wiki/Aspirin, January 25, 2010.
[2] Joseph A. DiMasi, *New Drug Development in the United States 1963 to 1999*, 69 Clinical Pharmacology & Therapeutics 286 (2001).
[3] Biologics and recombinant biotechnology drugs are less expensive to develop but the sums are high enough that the analysis set forth *infra* for small molecules still applies.

rational agency is more likely to approve a drug if it represents a significant medical advance than if it is merely an incremental improvement of a marketed drug, or does not address a serious medical need.

Submitting a New Drug Application (NDA) for approval by the FDA is a risky endeavor because it is very difficult to predict which way the Agency will rule. The difficulty of obtaining FDA approval seems to shift based on the incumbent leadership and political climate. This barrier is related to a cultural climate within the FDA that is an unfortunate side-effect of political pressures which induce the agency to become overly conservative in its product approvals.[4] In particular, the agency tends to receive negative feedback for allowing products to reach the market that are later found to have adverse effects while rarely receiving such feedback for failing to avail various patient populations with new and often much needed pharmaceuticals.

B. Patents and the free-rider problem

While the public has funded much of the basic research and scientific training that has enabled advances in pharmaceutical therapy, market incentives have induced the organization of a private pharmaceutical development and commercialization infrastructure that has effectively brought these advances to market. Absent an enforceable patent, the huge costs of pharmaceutical innovation and regulatory clearance are easily expropriated by free-riders. Stated in the formulation of Dan Burk and Mark Lemley, the ratio of the cost of innovation to the cost of copying is high, perhaps the

[4] See Richard A. Epstein, *Overdose: How Excessive Government Regulation Stifles Pharmaceutical regulation, pp. 109-132 (2006)*

highest of any industry.[5] In contrast, the software industry has the lowest ratio due to the lack of capital equipment needed for coding and nearly negligible fixed and marginal manufacturing costs. While the cost of pharmaceutical discovery and clearance of regulatory barriers is measured in the hundreds of millions, the cost of free-riding is measured in only millions. For example, approval of an ANDA for a generic drug takes only about 3-5 years and about $500,000, not including patent litigation costs. [6,7,8] Following approval, a pioneer drug (a "New Chemical Entity" or "NCE", as opposed to a generic drug) requires substantial marketing expenditures to educate doctors and patients about the existence and benefits of the drug and, as regulated by law, the risks of the new drug. If the intended use is for purposes other than the use presented in the NDA, additional clinical studies and supplemental NDAs are required.[9] Improper off-label promotion is vigorously policed. For example Pfizer recently paid $2.3 billion in settlement of civil and criminal charges for off-label promotion of four drugs.[10] In contrast, the launch of a generic drug requires far less expenditure because the generic drug can rely on safety and efficacy data submitted by the pioneer company. Furthermore, the public has already been educated about the existence, benefits and risks of the new drug and thus the bioequivalent generic drug. The pioneering company may already have filed supplemental NDAs to clear promotion for multiple indications.

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[5] Dan L. Burk and Mark A. Lemley, *Policy Levers in Patent Law*, 89 Va. L. Rev. 1575 (2003)

[6] ANDA stands from "Abbreviated New Drug Application", which is required for approving generic drugs under 21 U.S.C. §505(j) and requires proof that the generic is chemically and biologically equivalent to the pioneer drug.

[7] Peter Barton Hunt, Richard A. Merrill, and Lewis A. Grossman, *Food and Drug Law: Cases and Materials*, 764 (2207).

[8] Patent litigation costs are increased by the policies of the Hatch-Waxman act that encourage litigation.

[9] Sanctions against pharmaceutical companies and drug salespersons have been increasing of late

[10] See "Pfizer to pay $2.3B in largest health-care fraud settlement",http://news.bostonherald.com/business/healthcare/view.bg?articleid=1194925, as of January 26, 2010.

As a result of the enormous NCE development costs, the initial marketing costs and the disparity in profitability between NCEs and generics, drug companies rely on patents to guarantee profit margins large enough to recoup costs on NCEs and to deliver a favorable risk-adjusted rate of return. Thus, patents are widely considered to be the life-blood of the pharmaceutical industry. As a general rule, no rational drug maker will pursue the cost of developing a pharmaceutical molecule or other composition without first obtaining a patent on the composition, or other protection from the state. In economic terms, without pharmaceutical patents, there would be no first-movers. Without first movers, there would be no drug development industry, and no new drugs to benefit the public.

II. Current state-provided barriers to entry

A. The Food and Drug Administration

Patents are not the only form of government-sanctioned barrier to entry. Rebecca Eisenberg suggests that the FDA has evolved from an agency tasked solely with product safety to one tasked with promoting and managing pharmaceutical innovation. [11,12] Eisenberg catalogues the regulations administered by the FDA that benefit market

[11] The Food, Drug & Cosmetics (FD&C) act was passed in response to the 1937 deaths of 105 patients poisoned by the antibiotic Sulfanilamide formulated with diethylene glycol; see, Wax, PM. "Elixirs, diluents, and the passage of the 1938 Federal Food, Drug and Cosmetic Act." Ann Intern Med. 1995 Mar 15; 122(6):456-61.

[12] Since 1962, the FDA has been charged with not just ensuring that drugs are safe, but that they are effective. Due to the cost/benefit analysis inherent in the therapeutic use of pharmaceuticals, these issues are intimately entwined.

incumbents.[13] These benefits include (i) regulatory hurdles that need to be cleared by generic competitors and (ii) pseudo-patents granted by the agency.[14]

The current FDA pseudo-patents are: (i) seven years of post-approval market exclusivity provided under the Orphan Drug Act of 1983 [15], (ii) five years of data exclusivity for "new chemical entities" [16], (iii) three years of market exclusivity for products that are changed (e.g., in dose or formula) in ways that require additional clinical testing under the Hatch-Waxman Act of 1984, and (iv) six months of added exclusivity for conducting pediatric trials, under the Food and Drug Modernization Act of 1997. Eisenberg correctly notes that these provisions establish a role for the FDA in promoting pharmaceutical innovation, as opposed to its more traditional safety and efficacy functions.

There are two legal nexuses between the FDA and the United States Patent Office. First, the FDA will not approve a generic drug during the patent term of a pioneer drug.[17] Second, under 35 U.S.C. §156, the patent office will extend the term of a

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[13] See *Id.*, at 480.

[14] This raises an interesting question: is there Constitutional sanction of this power? In my view, Constitutional authority for these actions can be found in the patent clause of Article I, Section 8. Accordingly, the Constitutionality of pseudo-patents is limited to the extent that they promote the useful arts. Thus, a grant of a 50 or 100 year exclusivity period, as is the new norm with trademarks, would probably be unconstitutional.

[15] The Orphan drug act, 21 U.S.C. §§525-528, provides market exclusivity for drugs that treat conditions that affect less than 200,000 people in the US or where there is no reasonable expectation that costs will be recovered from sales. The act also includes tax credits as a further incentive. The act is widely regarded as a success in furthering its goals.

[16] Data exclusivity refers to a period in which the pioneer company's safety and efficacy data is kept confidential. As a result, generic competitors must do their own clinical testing to enter the market during the data exclusivity period, as opposed to merely showing biological and chemical equivalence of the generic product.

[17] Under 21 U.S.C. §505, a generic manufacturer must certify to noninfringement or invalidity of patents listed by the pioneer company. This is considered an act of patent infringement and an automatic stay of approval results if suit is filed against the potential infringer within 45 days.

pharmaceutical patent. The term of the extension is up to half the period of clinical research and the period of regulatory review by the FDA, for a maximum of 5 years.

B. The patent system

With the possible exception of orphan drugs, these pseudo-patents are generally of insufficient term to replace the investment-recovery function of patents in the pharmaceutical industry. Although not conclusive evidence, I am unaware of any NCE that has been brought to market absent patent protection outside of the orphan-drug act.

The patent system seeks to promote the useful arts by providing limited-term monopolies to inventors.[18] Because of the charter to promote the useful arts, most courts and commentators view patent rights as a utilitarian tool to promote progress. Accordingly, patent rights are not seen as natural right in property, despite having the attributes of personal property. The patent laws are treated by the courts as a law of general applicability. The same set of rules is used to decide the validity and infringement of patents for the full range of technologies including mechanical devices, software, and chemical arts.

Even among proponents of the patent system, there is a general lack of clarity about the exact benefits of patents. Patents provide, in varying combinations, an incentive to *invent*, an incentive to *disclose* technological advances, and an incentive to *innovate* (to commercialize a product).

Patents on pharmaceuticals provide the most compelling match between the goals of the patent system and the economic realties. Patents clearly provide an incentive to *invent*. By making pharmaceutical discovery profitable through protection from free-

[18] See U.S. Const. art 1 §8.

riders, patents provide incentive for investment in research. This investment pays the salaries of scientists and funds the purchase of research equipment and reagents that are needed to develop biological assays, test as many as five million chemical compounds in a compound library, synthesize and test derivatives of "hits" to discover a "lead" compound, and test the lead compound *in vitro* and in animal models. High throughput screening is the automated biochemical or cell-based testing of a chemical compound library ranging is size from about 200,000 to several million compounds. A typical high-throughput screen may result in about 2500-5000 hits.[19] Of these, an average of about 250 will enter preclinical testing, including animal testing.[20]

At this stage, the lead compounds are closely guarded secrets, lest a competitor gain hold of this information, which is essentially a highly distilled form of research investment.[21] A competitor could use the structure of the lead compounds to design-around the intellectual property of the innovative company. In addition, competitors may scan patent filings to discover those markets, diseases, and biological targets (e.g., enzymes and receptors) that are being pursued by esteemed market participants, thus gaining the benefit of the inventor's market research and early biological research.

Nonetheless, it is precisely at this stage of research that pharmaceutical companies *disclose* their inventions in hopes of obtaining a patent. In practice, patent applications are published about 18-months after filing. While it is possible to keep patent applications secret until issue in the United States, this is not possible in foreign

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[19] Based on Data from the Tufts Center for Drug Development, Tufts University, (2005).
[20] *Id.*
21 In general, information is a public good. Like other public goods such as national defense, drug discovery information suffers from the same problems of free-riding, and has a similar philosophical basis for using public force to prevent free-riding and ensure production.

jurisdictions. Because the pharmaceutical industry is a global pursuit, almost all patent applications in the industry are published. As a result, the possibility of patenting is a key driver of disclosure that advances the state of the art. The public benefits from this disclosure because academics and researchers working for drug competitors are able to use the findings in guiding their own research activities. For example, the competitors may use the information to identify promising targets or classes of molecules. The competitors are also put on notice as to what molecules are no longer patentable for lack of novelty, thus reducing wasted expenditures and the overall cost of pharmaceutical R&D.

Disclosure in a patent may have a knock-on effect on further disclosure. Once a patent filing discloses the identity of a drug, corporate researchers may be allowed, or even encouraged, to publish research and preclinical data related to the compound. A policy of allowing publication enables a drug company to increase awareness of potential new drugs. Companies that encourage publication in peer-reviewed journals may benefit by enhanced retention of higher quality researchers. In some cases, academics become aware of new compounds through peer-reviewed publications and use these compounds as a research tool to better understand biological pathways.

After the preclinical testing stage, the compound must be further scaled-up and tested in man. For approximately every 250 compounds that enter the pre-clinical stage, only one will successfully pass the FDA regulatory gauntlet and enter the market. As noted above, the average cost of an NCE is measured in hundreds of millions of dollars. Here, patents incentivize market participants to *innovate* by ensuring economic gain from the venture.

III. Deficiencies in the current regime for protection of pharmaceutical investment

A. Benefit to the public rationale in patent law and its misapplication to pharmaceuticals.

In order to be eligible for a patent, an inventor must disclose the invention in sufficient detail to prove that she was in possession of the invention at the time of filing and to enable one of ordinary skill in the art to make and use the invention. 35 U.S.C. §112. The invention must be novel under 35 U.S.C. §102 and nonobvious under 35 U.S.C. §103.

(i) *The Novelty Requirement and Incentives for Disclosure.* The rationale for the novelty requirement is twofold. First, inventions that are already in public knowledge, use, or commerce do not need the incentive of a patent to come to market. Second, the public may come to rely on the free availability of these innovations. Withdrawing them from the public domain would be unfair to those relying on the availability of an innovation, destroy the value of past investments, and discourage future investment by fostering uncertainty. For example, a manufacturer may combine multiple components into a new product, only to later find that one of the components is no longer freely available, resulting in the withdrawal of the entire combination product from the market. For these reasons, where the public nature of an idea is questionable, the inventor bears the risk. See, *In re Hall*, 781 F.2d 897 (Fed. Cir. 1986) (single copy of a prior-art reference indexed only in a remote library found to defeat novelty).

The patent law creates incentives for early filing. These incentives have both positive and negative effects on the public weal. An inventor dedicates an invention to the public when she discloses or uses it publicly and does not file a patent application in

the course of a year, as provided by 35 U.S.C. §102(b). A major policy goal of section 102(b) is to promote early filing of patent applications. See, *Pennock & Sellers v. Dialogue,* 27 U.S. 2 Pet. 11 (1829).

Publication of a pharmaceutical patent application does not benefit the public nearly as much as a safe and effective drug, on the market and available for use by needy patients. Patent publication notifies competitors and starts the patent-term clock running, thus reducing expected return on investment for new drug research. If the running of this clock prior to approval erodes enough of the patent term, the owner of the patent is likely to abandon the drug development project as unprofitable. As a result, a policy of requiring early filing for pharmaceutical patents *decreases* the chance that the public will benefit from the invention.

Disclosure is also used defensively. Drug researchers often produce and test a large number of analogs that are chemically related to a lead compound. By disclosing the structure of all of these compounds and the results, the incentive of others to develop closely related molecules is reduced. Due to the disclosure, the patent office would find that the related molecules are anticipated by or obvious over the disclosed variants, and thus unpatentable. For this reason, research activities by competitors within this chemical space will be sharply disincentivized. With respect to the public benefit, such disclosures have both positive and negative effects. One benefit is scientific: academic and industrial scientists can use the knowledge as a starting point to gain new knowledge. For example, molecules disclosed in a patent application can be used in pharmacological research to better understand biochemical pathways. The public also benefits to the extent that the profitability of bringing drugs to market is enhanced by keeping out

competitors that might free-ride on expensive research through minor modifications of the subject molecules. The negative consequences of such disclosure are discussed below.

(ii) *The nonobviousness requirement.* The nonobviousness requirement blocks the issuance or enforceability of patents on inventions that are novel, "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". 35 U.S.C §103.

The Supreme Court has recently clarified the law of nonobviousness. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007). *KSR* substantially liberalized the previous test. Prior to *KSR*, the Court of Appeals for the Federal Circuit required that for a finding of obviousness, there must be some teaching, suggestion or motivation in the prior art that would guide a person of ordinary skill to arrive at the claimed invention (the TSM test). The rule of *KSR* allows for "common sense" or "market forces" to bridge the gap between the prior art and the claim.

The claimed invention in *KSR* was an adjustable automotive acceleration pedal that included an electronic position sensor mounted on a pivot of the pedal mechanism. United States Patent No. 6,237,565. The Court found the invention obvious over a combination of prior art references teaching an adjustable automotive pedal and a pedal with an electronic position sensor. In reaching this decision, the Court held that market forces could prompt a person of ordinary skill to implement a predictable variation of the

prior art, rendering that variation obvious. *Id.*, at 4. The car manufacturers had already pointed to the desirability of electronically actuated pedals and it was only a matter of time until a designer combined this trend with an adjustable pedal. The Court cautioned against issuing patents that would occur in the "ordinary course" lest they retard progress, rather than promote it. *Id.,* at 5. Thus, the determination of obviousness hangs on a very subjective, imagined, development time in a hypothetical world in which the inventor is absent. The *KSR* standard trades the predictability of the TSM for flexibility in making utilitarian economics-based decisions.

The nonobviousness requirement acts as a policy filter to block patents on technologies that would have become available to the public without the benefit of the patent system. For most classes of invention, this logic is compelling. Where the invention is a minor, easily foreseeable, modification of a known mechanical device, industrial process or software algorithm that requires trivial investment in research and development, the public is harmed by the issuance of a patent because the inventor may now seek monopoly rents, thereby denying the consumer surplus that the public would have otherwise enjoyed.

However, the nonobviousness requirement is far less compelling where there are major obstacles to commercialization. Here, the ordinary course is a route that bypasses the market and the consumer. The pharmaceutical industry faces the twin obstacles of exceptionally high research costs and unpredictable regulatory clearance. As a result, the default condition is non-development of the product. An invention that involves a minor modification to a pharmaceutical compound may be denied a patent for lacking sufficient inventiveness, perhaps because the prior art suggested that making that particular

modification was obvious to try, or it was one of a small number of modifications that could be made. As a result, this invention will not receive a patent, and will likely never reach the consumer in the ordinary course for lack of protection from free-riders. The policy goals of the patent system and the public health are misaligned because there will be many instances where the difficulty of conceiving an invention does not coincide with the benefit of awarding a patent and the corresponding boost in the chance of the invention reaching the patient.

Furthermore, the market forces rationale of *KSR* is not applicable to pharmaceutical compounds. For pharmaceutical compounds, the market forces are unmet medical conditions and are almost always known ahead of time. The reward for inventing a new treatment for one of these well-known medical conditions should not be diminished by knowledge of the condition. Rather, our laws should seek to promote development of such products over "me-too" drugs of lesser value to the public.

The law of obvious does account for some economic factors. Evidence showing that there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048 (CCPA 1976). Because the pharmaceutical arts are much less predictable that the mechanical arts, the predictability doctrine creates a sliding scale of obviousness. On the obverse side, a reasonable expectation of success will support a finding of nonobvious. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986). As a net result, through either fact or insufficiency of proof, at least some potential pharmaceutical inventions will fall to the nonobviousness requirement.

In *Altana v. Teva*, a post-*KSR* decision, the Court of Appeals for the Federal Circuit clarified the role of prior art structure and potency disclosure in obviousness determinations. *Altana Pharma AG v. Teva Pharms*. USA, Inc., 566 F.3d 999 (Fed. Cir. 2009). The plaintiff's own prior art patent reference disclosed a variety of compounds including the starting point compound used in the synthesis of a variety of related compounds, including the compound of the claim at issue, an ulcer medication known commonly as Protonix®. In the prior reference, the starting point compound was disclosed to have one of the better potencies of the compounds made and tested. In denying the plaintiff's request for a preliminary injunction, the court found that there was a substantial argument that the claimed compound was obvious because of the prior art teachings related to the starting point compound. This decision highlights how prior art disclosures of compounds can foreclose development of structurally related, but ultimately commercially viable and medically relevant compounds. The *Altana* decision being a decision on a motion for preliminary injunction, it is possible that Protonix® may be patentable based on additional facts. Nonetheless, the decision illustrates the height of the nonobviousness hurdle. A drug discovery firm is thus placed between the Scylla of a high-probability search for drugs closely related to the prior art with a low probability of nonobviousness, and the Charybdis of a low-probability search for drugs in uncharted territory with a high probability of nonobviousness.

At the root of this policy disconnect is the stage of the R&D process at which obviousness is determined. Patents reward early-stage R&D, whereas the majority of expense and public benefit resides in the later development stages. Researchers typically file patent applications early in the research stage and the patent office determines

patentability based on these filings. A typical pharmaceutical patent application will disclose the structures of novel compounds, routes for synthesis of these compounds, and some biological data used to infer that the compounds may have utility in fighting some disease. Typical biological data is generated *in vitro* (in the modern equivalent of a test-tube) or in an animal models. Such data satisfies the utility and enablement requirements of the patent law, as currently interpreted. *In vitro* data, such as the potency data in *Altana*, is more rapidly produced and much less costly than extensive animal testing and clinical testing. Yet the predictive value of this data is poor, otherwise the cost of pharmaceutical development would not be so high. This is so due to lack of good animal models, and poorly understood genetic, epigenetic and environmental variability among human patients. Compounds that are optimized in the laboratory for the easily measured parameter of potency are likely to fail in later stages due to poor performance in system-level parameters of toxicity, and pharmacokinetics. [22] Scale-up and formulation of the compound present further barriers. Thus, even if a person of ordinary skill in the art could have made the invention, that person could not necessarily have developed it into an approved drug.

In a perfect world, researchers would present phase III human trial data to the patent office for evaluation. The patent office would then ask whether there was utility (was the drug efficacious and reasonably safe?) and whether the drug was new and nonobvious. Since taking a drug to this stage is so fraught with risk, presumably the nonobviousness threshold would be easier to cross for the patentee.

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[22] Pharmacokinetics are measures of how well the compound remains in the body in an active state.

In the real world, to require such testing prior to patenting would be counterproductive. Pharmaceutical firms rely on patent approval, or at least a promising patent prosecution, before embarking on the most expensive portions of the clinical testing process. To delay the approval process would dramatically downshift the economic drivers of the industry. Furthermore, keeping the identity of the molecules secret for such an extended period would be fraught with risk of accidental disclosure or discovery and disclosure by another firm.

B. The example of "trapped treasure"

The mismatch between the public benefit doctrine and pharmaceutical industry economics manifests itself as "trapped treasure". During the course of industrial research, numerous patent filings may be made, each disclosing numerous compound analogs. This practice exists for several reasons: (i) patent filings must be made early in the research process lest others patent the discoveries first, (ii) due to the unpredictability of the art researchers are unable to be certain which analog will be the ultimate development compound, and (iii) sufficient claim breadth must be supported by the disclosure to give protection against minor changes by competitors. All the non-developed compounds that are disclosed then become prior art to later researchers. Academic researchers also contribute to the prior art when they publish additional molecules in patents or scientific papers.

The result of these prior-art generating activities is the donation of knowledge of these potential drugs to the public. Although the state of science is advanced, incentive to further research or develop these drugs and their obvious analogs is destroyed. Without a patent or perhaps an orphan-drug pseudo-patent, the economic incentive to run

the regulatory gauntlet does not exist. As time goes on and scientific research progresses, such molecular structures accumulate in the prior art. In a sense, these drug candidates are forever trapped in the amber of scientific advance. To make matters worse, one can imagine that some number of decades in the future, advances in systems biology, drug-testing automation, and computational chemistry will place the majority of drug-like molecules in the prior art.

Although difficult to quantify, negative economic consequences include increased R&D expenses in the quest to find molecules that are not just more efficacious but *also* novel and sufficiently nonobvious. Additionally, patient health is impacted. Clearly, the novelty and inventiveness of the molecule itself is of little direct benefit to the suffering patient. Inventiveness in chemistry and biochemistry advance the technical arts, but correspond far from perfectly with innovation in medicine.

The trapped treasure concept encompasses nonconventional medicines such as herbal medicines, vitamins, or "nutraceuticals." These medicines are not new; some have been known for hundreds of years. Lack of novelty makes them unpatentable. Occasionally trials are run by government or charitable research institutions but overall, because they are unpatentable, clinical data on these substances is scant. As a result, the public overuses many useless or even harmful substances and, perhaps more importantly, under-uses useful ones. The political standoff between the nutritive "supplement" lobby and the FDA results in a highly unregulated supplement market. As a result, the safety, quality, and purity of supplements are sub-optimal, with a likely negative impact on consumer's health.

Numerous news stories are published each year announcing publication of scientific articles, some of which are published by scientists at reputable institutions in reputable scientific journals, claiming potential medical breakthroughs involving unpatentable subject matter. These potential breakthroughs rarely reach the mass market because they cannot compete with the conventional prescription drugs status in several respects. First, funding and incentive do not exist to perform extensive clinical trials on these substances. The cost per patient for a phase 3 clinical trial is estimated at $26,000.[23] As a result, these potential therapies do not carry the same medical gravitas as an FDA-approved new drug. Second, the incentive for a producer to invest in a marketing campaign to spread knowledge of the advance to doctors and patients is small in comparison to conventional therapies. Third, doctors and risk-adverse consumers may be less likely to place trust in the potency and lack of adulteration of commercially available products.

Although any given supplement claim may not be true, there are at least some that are valid clinical hypotheses backed by sound science. Of these hypotheses, it is likely that at least some would be found to be supported if tested. The public is likely to never have the benefit of these potential medicines.

As a counter-example, I am aware of one supplement that is currently in clinical trials. In June of 2009, scientists at a Cambridge University spin-out company announced that they had shown that a lycopene supplement (a tomato extract) was effective at reducing the amount of oxidized cholesterol in the circulation of human

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23 "Phase 3 Clinical Trial Costs Exceed $26,000 Per Patient", http://www.lifesciencesworld.com/news/view/11080, as of January 26, 2010.

subjects.[24] Based on rudimentary studies, the company hypothesized that the supplement may be more effective than statins, a class of conventional cholesterol medications. One can speculate that no safety problems are to be found with a substance that is found in tomato paste. If this were true, the health and economic impact could be enormous. To evaluate the truth of these health claims, resources on the order of those spent for long-term clinical trials on Lipitor® would be required, which enrolled over 2000 patients.[25] Additional, post approval trials have also been performed for Lipitor.

Investing in such trials for lycopene could be a poor business decision because competitive products are already on the market.[26] Any benefit from the tens of millions of dollars spent on clinical trials and the millions of dollars needed for a promotion campaign to compete with statins would be captured to a large degree by theses competitors. Nonetheless, according to clinicaltrials.gov, there is a phase III clinical trial currently recruiting patients in the United States. [27] It remains to be seen if the trial is sufficient for FDA approval, and how Cambridge Theranostics will appropriate the value of the product, which is apparently nothing more than tomato extract in pill form. Perhaps the five year NCE exclusivity period is sufficient reward. The source of the funding is also unknown; the trial may be government-sponsored. Even if this one product is approved and profitable, the business-model of clinical testing of supplements seems to lack viability in the long-run.

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24 The company is Ateronon, see the Ateronon website at www.ateronon.com. Lycopene is the red substance found in tomatoes.
25 The 2000 patients are for a published pre-approval trial. Additional post-approval trials have also been performed.
26 Similar products are available from, for example, www.vitaminshoppe.com.
27 "Trial of Lycopene/Ateronon for Secondary Prevention of Coronary Heart Disease", http://clinicaltrials.gov/ct2/show/NCT00939237, as of January 26, 2010. The sponsors and collaborators are listed as "Brigham and Women's Hospital and Cambridge Theranostics".

As appreciated by Chinese herbal healers, many of these substances are only effective in combination. However, for FDA approval of a combination, each member of the combination must be tested separately; hence further raising the cost of clinical trials. Thus, like the aforementioned trapped treasure, combination therapies that include multiple conventional drugs, or conventional drugs in combination with supplements or traditional herbal medicines, are potentially valuable but unpatentable compositions for which the vast majority of the benefit does not inure to the public.

IV. Potential mechanisms for reconciling pharmaceutical innovation policy with the patent law

Several potential policy changes may harmonize regulatory and patent law. The solutions explored here fall into the following categories: lowering the barrier to regulatory approval, raising patent or pseudo-patent barriers to free-riders, and directly rewarding drug development with grants or prizes. Each presents its own advantages, liabilities, and barriers to adoption. As with any proposal to alter property rights, one must evaluate both administrative costs and incentive effects.

A. Solutions that lower the regulatory barrier for firms

A class of solutions lowers the regulatory barrier to entry for pharmaceuticals. With a lower barrier, the role of patents would then become like that for a more conventional industry in which patent protection is a desirable, but not mandatory, barrier to entry. In those industries, firms routinely develop and market products that are off-patent or unpatentable due to the existence of prior art. Barriers to entry such as goodwill, costs of production and advertising expense allow for recovery of R&D

investment. Firms can compete on factors such as operational excellence or customer intimacy rather than from a monopoly position. In a reduced-barrier environment, pharmaceutical firms would develop unpatentable molecules. The public would benefit from the availability of these medicines and the consumer surplus associated with non-patented products.

Policy changes that lower the regulatory barrier fall into two classes: (i) a laissez-faire approach that de-emphasizes FDA requirements and (ii) an expanded-government approach in which the government takes primary responsibility for funding clinical trials.

(i) Eliminating the efficacy requirement.

Richard Epstein proposes that eliminating the safety-monitoring function of the FDA would, on the whole, benefit patients rather than harm them.[28] Epstein's rationale is that the FDA harms more patients by withholding drugs from the market than it protects by keeping inefficacious drugs off the market. The FDA behaves this way because the political effect of widely reported adverse drug safety incidents outweighs any political effects from the relatively invisible suffering of patients for whom potential drugs are withheld. Further, the new drug approval process is structured to prove statistical efficacy for a hypothetical average person. As a result, the process denies non-average people (which we all are) and their doctors the option of exploring the full range of potential medicines to best suit their particular biological situation. Individual patients also vary in their tolerance for risk and side-effects based on their medical situation and constitution, whereas the FDA must use a uniform evaluation of risk. Patients and their

[28] *Overdose,* at 113.

doctors are in a better position to evaluate known risks and rewards on a case-by-case basis.[29]

Under Epstein's proposal, the barriers to entry may be greatly reduced. Firms would need only to run safety trials and whatever efficacy studies are needed to convince the medical community of the benefit of a new drug. Because this lower barrier would increase the breadth of available drugs, both patented and unpatented, competition in the industry would heighten, and the cost of medicine to the consumer would be lowered. A further advantage of this approach is that the costs of administering the policy are negative. In the scheme, patents would remain important, but less so. Increased competition and lower barriers would increase the importance of breadth in pharmaceutical patents because competitor work-arounds based on small changes to the drug molecule would become approvable and thus economically feasible. Other potential competitive devices would come to the fore, including marketing, and competition for the endorsement of the scientific community.

A negative aspect of this proposal is that both reliable safety and efficacy data are required to evaluate a cost/benefit ratio. Without this data, physicians will be unable to evaluate safety claims. Most physicians will not be in a position to evaluate the scientific studies that are performed.

As a result, the market would likely respond with private certification agencies. A much wider variation in certainty with respect to safety and efficacy than we are accustomed to would ensue. Alternately, it is possible that the resulting free market and tort-liability forces may demand a level of clinical trial expenditure that is no less than

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[29] *Id., at 51.*

demanding than current FDA requirements. This is unlikely given that the FDA currently rejects many drugs. Presumably, the applicant firms would have marketed the drugs had the FDA approved them.

Regardless of the merits of this approach, Epstein's liberal vision is not politically tenable given the current political climate and political structure of the United States. Some unscrupulous firms would promote products using poorly conducted efficacy studies. The resulting scandals would lead to renewed calls for re-regulation because these failings would become well known and the successes of individual patients and doctors under the liberalized system would remain relatively quiet. In other words, the benefits of the system are diffuse, while the liabilities are concentrated. Furthermore, the pharmaceutical companies may discover that their profitability is seriously impaired without the regulatory moat to protect them and join the call for re-regulation.

(ii) Government sponsored trials.

Another way to reduce the regulatory barrier is through government-funded trials. To some degree, this occurs today. The National Institutes of Health does contribute, through grants, to the cost of testing drugs that it deems medically important. This approach would not eliminate the regulatory barrier, but would shift the risk of failure to the taxpayer, thus lowering the barrier for pharmaceutical firms.

To extend this approach to cover the majority of drug discovery efforts would be extraordinarily costly. Further, moral hazard would ensue; firms would be less careful about evaluating risk/reward ratios in performing clinical trials where the risk is shifted elsewhere. A conflict of interest is present: in disallowing a new drug, the FDA would be declaring that taxpayer money had been wasted, and may come under pressure from

lawmakers to approve certain drug applications. In general, drug development decisions would be subject to the vagaries of politics. Development money would be allocated in large part to the most vocal patient advocacy groups. For example, drugs for chronic diseases such as HIV may be developed at the request of vocal groups while the relatively unorganized victims of acute infections with drug-resistant bacteria are left to silently die. This would occur despite the fact that drug-resistant bacteria are the greater public-health problem.

B. Solutions that raise the regulatory barrier to free-riders.

The regulatory barrier to second-moving free-riders may be raised within the patent system or within the FDA regulatory system. Such barriers evaluated here are: expanded pseudo-patents, revisions to the law of obviousness, and the creation of a new type of patent. Ideally, the barrier should be raised in a manner that incentivized clearance of the regulatory hurdle for both inventive and obvious medicines.

(i) Expanding the scope of pseudo-patents

A regulatory approach to accomplish these ends would be to increase the term of market or data exclusivity for new chemical entities. By increasing the period of exclusivity for NCEs from the current five year period to a longer term, firms will have sufficient incentive to run the regulatory gauntlet, even absent a patent. One should not make this period so long as to obviate the patent system, for we still wish to reward technical innovation. At an extreme, the pseudo-patent term could be extended for 17 years (the traditional term of a U.S. patent [30]) and an additional term of patent life could

[30] Due to international harmonization, the term of a U.S. patent is now 20 years from filing rather than the traditional 17 years from issue. The effect is similar because there is a 3 year application pendency target,

be tacked-on for innovative products. A guidepost for choosing a term for our extended pseudo-patent is found in current negotiations between the biotechnology companies and generic manufacturers over pending legislation that would authorize biosimilars (a biosimilar is equivalent to a generic drug for recombinant protein pharmaceuticals). The Biotechnology Industry Organization has proposed that a pseudo-patent term of 14 years of data exclusivity is necessary to recoup industry investment in biosimilars[31].

A similar extension of term could be applied to the orphan drug act. In addition, the scope of the act could be expanded to cover a potential drug for any unmet medical need, without regard to market size or patient population.

The use of this policy lever has the advantage that the administrative mechanisms are already in place. The change is specific to the pharmaceutical industry and so does not implicate traditions of general applicability in the patent law. The reward is directly tied to the desired goal of developing approvable products.

(ii) Revision of novelty and obviousness standards.

As noted above, the law of obviousness, while rewarding creativity and serendipitous discovery, does not reward that which is most valuable: clearing the regulatory and marketing hurdles to thereby bring drugs to the patient. This deficiency may be remedied through improvements to the patent law implemented from the bench or by statute.

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codified in policy as a patent term adjustment under 35 U.S.C. 154(b) for patents that are issued more than 3 years from filing.

[31] Press Release: "BIO Calls For 14 Years of Data Exclusivity in Any Follow-On Biologics Legislation," http://www.bio.org/news/pressreleases/newsitem.asp?id=2007_0503_01, May 5, 2007.

Patents are authorized by the Constitution to promote the useful arts. The distribution of rights to patentees in order to promote the arts is best done with an evaluation informed by the economics of the industry in which the product is sold. The judiciary has chosen to avoid this inquiry, treating patent law as a law of general applicability. One reason is that modern patentability doctrines have their root in the early industrial revolution [32], a time when relevant economic variation in industries was not as pronounced. While the lessons drawn from these early cases may be correct, the law needs to be flexible enough to accommodate the economic variables of different types of inventions. Confronted with modern industries such as microprocessors, software and pharmaceuticals, the courts have chosen to limit economic inquiry in patent validity challenges.

The trepidation of the courts in thoroughly considering economic consequences of nonobviousness decisions on a case-by-case basis is justified. Modern antitrust cases are a good guidepost to the absurdly high administrative costs that may result from detailed economic inquiries. One way to reduce the administrative impact would be to announce broad rules on an industry-by-industry basis. Yet even this approach may be problematic when inventions are interdisciplinary or industry boundaries are poorly defined.

These general observations notwithstanding, secondary indicia of nonobviousness of an economic nature are currently permissible forms of evidence. These indicia include, but are not limited to, long-felt need, failure of others, and commercial success. *Graham v. John Deere Co*. 383 U.S. 1 (1966). Secondary indicia will surely become

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[32] *Hotchkiss v. Greenwood* 52 U.S. (11 How) 248 (1851)

more important in view of *KSR* and the associated decrease in prominence of the clearly defined TSM test.

In the field of pharmaceutical patents, a realization that promoting the useful arts lies mostly in overcoming the risks inherent in clinical testing would go a long way toward reconciling the law of patentability with promoting medical progress. Accordingly, the patent office and the courts should be liberal in accepting evidence of expected clinical superiority as proof of nonobviousness. Otherwise, inventions that would otherwise benefit the public through private development efforts will be left in the amber of the public domain. The classification of chemistry as an unpredictable field should give rise to a presumption that pharmaceuticals inventions are nonobvious.

(iii) Creating a new type of patent to reward later-stage pharmaceutical development.

The problem may be addressed in a more direct manner through the creation of a new type of patent that directly rewards investment and risk taking in clearing the FDA regulatory hurdle.

Currently, where a medicine is not novel, but a new use is discovered, the patent office may grant a method of treatment claim. These claims have the general form: "A method of treating [condition X] by administering a therapeutic amount of [composition Y]." Medical practitioners are immune from suit for infringement for performance of a medical activity. 35 U.S.C. §287(c). A patentee must therefore sue the manufacturer of the medicine that is used for the claimed purpose for contributory or inducement of infringement under 35 U.S.C. §271(c). The difficulty of this type of suit is greater than

for a direct infringement suit because the manufacturer of the drug may defend by proving that there is a substantial noninfringing use.

Even if method patents were highly enforceable, an additional problem would remain. Where the prior art teaches or suggests such a use for composition Y, the claim is unpatentable. If, for such claims, the patent law were to treat only FDA-approved clinical trials as prior art to pharmaceuticals, the patentability of any compound would not be foreclosed until the scientific research on the compound was sufficient. At that point, further incentive to develop the compound would not require the benefit of a patent and the interest of patients would be fully served by the patent system. Unfortunately, this approach suffers from the problem that a patentee could claim a known use of a known compound without adding any value to the public.

Alternately, the problem of known but untested uses could be addressed with a further claim formalism: "The clinically proven method of treating [condition X] with [composition Y] comprising administering a therapeutic amount of [composition Y] to a patient with [condition X]." Here, the claim contains an express plea for evaluation of patentability based on development-stage discovery. Issuance of such a "clinical patent" would be evaluated in relationship to reduction of uncertainty in the medical field, rather than the unlikelihood of the discovery. Only clinical data could be used as prior art against such a claim and enablement of the claim would require clinical proof at the time of filing.

What level of clinical proof should be required? If we set the standard too low, patents will be captured by firms that have not sufficiently contributed to the medical arts. On the obverse, if we set the standard too high, firms will not be awarded a patent

until after they have undertaken the expense of full clinical trials, a result that is unlikely if the issue of patent is not substantially certain. The possibility of multiple firms racing to complete clinical trials to grab the patent would waste resources and incent firms to perform clinical trials of inferior quality. Absent a bright-line rule, the courts would be left to prescribe the proper inquiry.

Assume that two companies succeed in developing an otherwise unpatentable drug and both seek patent protection. To whom should we award the patent? In current patent law this problem is solved through the concept of priority, in which the first to conceive and diligently reduce the invention to practice is awarded a patent over one who later conceives or earlier conceives but is not diligent. The priority system is effective in distributing rights but is imperfect in that R&D efforts are often duplicated. For clinical patents, a similar concept may be employed. The clinical patent will go to the first to file a notice of intent to perform the clinical testing. The filing of the notice will then trigger corresponding diligence requirements. A firm that is second to file could then unseat the first party via an administrative or legal proceeding to prove lack of diligence. If multiple parties have initial or secondary priority, the rights could be awarded by auction or lottery.

In an attractive scenario, the FDA or NIH (National Institutes of Health) could request that a particular therapy be tested. The exclusive rights to test and market the drug would then be auctioned to the highest bidder. As before, lack of diligence is grounds for wresting the right of exclusivity from the winner. For example, if significant controversy existed over the use of a nutritive supplement [33] in preventing heart disease,

[33] For example, see the lycopene example above.

the FDA could auction the right to market the supplement as a prescription or over-the-counter drug. This right would come with the ability to make the tested health claims for the substance. Currently, supplements are not allowed to claim, on labels or in marketing materials, that the substance is effective in treating a disease or medical condition. Supplements are only allowed to make "structure-function" claims, such as "supports a healthy immune system".

The development of a new patent type leverages existing patent law administrative infrastructure but would require changes to the patent law to be implemented by statute. Because the clinical patent issues earlier in the development cycle than an FDA pseudo-patent under the current framework, the clinical patent will increase the amount of investment in clinical trials.

C. Solutions that alter the rewards

A third class of potential policy changes alters the risk/reward balance by changing the reward. For example, a payment may be made to winners of FDA clearance to boost reward and encourage risk taking. Potential prize systems have been discussed in the literature.[34] This approach is unattractive because of the central planning that it entails. How should the FDA judge the value of each product? The FDA is ill-suited to such determinations and is subject to political factors. When should the award be made? If the award is made at approval, there is no guarantee that the public will benefit from continued marketing of the drug. If not at approval, then on what timeframe should the awards be made?

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[34] Marylynn Wei, "Should Prizes Replace Patents? A Critique of the Medical Innovation Prize Act of 2005", 13 B.U.J. Sci & Tech L. 25

V. Conclusion

Drug research and development is an especially expensive and risky undertaking, while the end result, clinical knowledge, is easily expropriated by free-riders. The patent system has traditionally been used to counter the free-rider problem. However, the patent system lacks sufficient economic levers to yield proper incentive schemes in industries that vary in terms of risk and appropriability. Thus, current patent jurisprudence is based on an assumption that placing inventions in the public domain is of benefit to the public. In the field of pharmaceuticals, the opposite is true: public domain molecules are forever trapped in the prior art. Several remedies to the situation are explored. Two favorable remedies to this policy problem identified here serve to bolster the barrier to free-riders to allow development of innovative yet unpatentable drugs. These remedies are (i) extending the term of FDA-issued pseudopatents and (ii) implementing a new type of patent claim that is tied to clinical progress rather than research progress. Of these two potential remedies, the first is the easiest to implement.

Bibliography

Dan L. Burke & Mark A. Lemley, *Policy Levers In Patent Law*, 89 Va. L. Rev. 1575 (2003).

Terry Mahn & Margo Furman, The Role of Patent and Non-Patent Exclusivity Under the Hatch-Waxman Act, available at http://www.fr.com/practice/pdf/05-16-05%20_PatentandNon-PatentExclusivity.pdf.

Wesley M. Cohen at al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or not),* Natl. Bureau Econ. Res. Working Paper 7552.

Daniel J. Gifford, *How do the Social Benefits and Costs of the Patent System Stack up in Pharmaceuticals?*, 12 J. Intell. Prop. L. 75 (2004).

Diane. C. Renbarger, *Putting the Brakes on Drugs: the Impact of KSR v. Teleflex on Pharmaceutical Patenting Strategies*, 42 Ga. L. Rev. 905 (2008).

David D. Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 Food Drug L.J. 125 (2000).

Andrew Moody, *Patently Obvious: A Dual-Standard Solution to the Diverging Needs of the Information Technology and Pharmaceutical Patent Industries*, 39 Golden Date U.L. Rev. 71 (2008).

Rebecca S. Eisenberg, *The Robert Levine Distinguished Lecture Series: Patents, Product Exclusivity, and Information Dissemination: How Law Directs Biopharmaceutical Research and Development*, 72 Fordham L. Rev. 477 (2003).

Arti K. Rai, *Building a Better Innovation System: Combining Facially Neutral Patent Standards with Therapeutics Regulation*, 45 Hous. L. Rev. (2008).

Mark D. Shtilerman, *Pharmaceutical Inventions: A Proposal for Risk-Sensitive Rewards*, 46 IDEA 337 (2006).

Joseph A. DiMasi, *New Drug Development in the United States 1963 to 1999*, 69 Clinical Pharmacology & Therapeutics 286 (2001).