INTELLECTUAL PROPERTY

Fixing the Legal Framework for Pharmaceutical Research

The outdated Hatch-Waxman Act and judicial retroactivity challenge costly development of new pharmaceuticals.

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The cost of drug research and development (R&D) has increased from ~$230 million per drug in the early 1980s to $1.2 billion today, with R&D currently requiring about 10 to 15 years per drug (*1*–*4*). This investment of time and money cannot be sustained without a legal system that provides sufficient time to recoup the investment and to secure a reasonable return, as well as the ability to make important business decisions that remain correct over a long period of time. Pharmaceutical companies have historically relied on two kinds of market protection: (i) the exclusive ownership of their own clinical research and (ii) patents. However, the U.S. Hatch-Waxman Act (*5*), which is designed to strike a balance between innovative pharmaceutical research and access to generic drugs, is flawed. Further, U.S. courts sometimes retroactively change standards for patent protection long after large R&D efforts have been initiated, which increases the risk to defend and rely on patent protection.

The Hatch-Waxman Act

The 1984 Hatch-Waxman Act applies to pharmaceuticals, not biologic products. It allows producers of generic drugs to use, without cost, all preclinical and clinical data to support approval of the drug that were filed by innovator pharmaceutical companies with the U.S. Food and Drug Administration (FDA) (*6*). Five years after approval of a "new chemical entity" innovator drug, a generic company can simply reference the innovator's data to support the generic drug application (*7*–*9*). If the innovator company does not have a patent protecting the product or if a court rules the patent invalid or nonenforceable, the generic company can then obtain approval to sell the drug, simply by referencing the innovator data and submitting only enough data to demonstrate that the innovator and generic drugs are bioequivalent (*10*). Furthermore, the usefulness of a patent on a drug typically only begins after drug approval, and the FDA requires 10 to 15 years of preapproval R&D after a patent application is filed. So, in exchange for the forced sharing of data with generics, under Hatch-Waxman, innovators are granted up to five additional years of post–drug approval patent protection, but in no event can the patent extend more than 14 years after the drug approval (the "14-year cap").

How does this quid pro quo work in practice? The 5-year data exclusivity period was a political compromise 26 years ago during Hatch-Waxman negotiations without substantial supporting economic analysis. This period is vastly inadequate today and rarely covers the breakeven point for reimbursement of R&D costs. Because of this, new drugs are almost never developed without patent protection, which limits the number of new drugs created (as not all useful drugs are patentable).

For those few drugs that are developed without patent protection or that lose patent protection through court decisions, does the forced sharing of expensive clinical research data with generics amount to a federal taking of property from the innovator pharmaceutical company? The "Takings Clause" of the Fifth Amendment provides that "private property" shall not "be taken for public use, without just compensation" (*11*). In the past 26 years, the cost of drug development has increased sixfold, and the period of data exclusivity given to innovator pharmaceutical companies for new drugs is still half the period given for pesticides (*12*). Without a change to update the law to increase the period of data exclusivity, compensation from the government for the involuntary use of innovator R&D data files by generic companies to obtain drug approvals seems fair.

Once a U.S. patent is granted, which the Patent Office intends to take ~3 years, the patent has a term of 20 years after the filing date (*13*). However, as discussed above, under Hatch-Waxman, the new drug gets capped at 14 years of useful post–drug approval patent term. This creates the situation where a relatively unregulated, simple, inexpensive invention may receive 17 years or more of useful patent term, whereas more expensive and important pharmaceutical innovations get useful patent terms capped at 14 years (*14*).

Changing Requirements for Patentability

A patent application filed today on a pharmaceutical innovation will not be used to defend a market for about 15 years. What will the law look like in 2025? How can companies make long-term investment decisions that remain accurate over 15 years or more?

"The Supreme Court is reconsidering … what constitutes patentable subject matter. At what point does an idea pass from an abstract theory to a patentable invention?"

Under the U.S. Constitution, Congress makes laws, and the courts interpret and apply them. However, there may be little practical difference to a corporation between changing a law and changing the interpretation of a law. Both change the rules of the game. However, when Congress passes laws, they apply prospectively, whereas when courts reinterpret the law, the new interpretation is applied retrospectively to business decisions that occurred sometimes long before (*15*). When a significant change in interpretation of a statute alters the burden to prove patentability, it can convert valid patents into invalid patents, or invalid patents into valid patents. The former can eviscerate the value of research programs, and the latter can create increased infringement exposure. Both disrupt well-settled expectations, which can affect the outcome of long-term business decisions and can have an effect indistinguishable from a congressional change in law.

In 2007, the U.S. Supreme Court issued the landmark decision *KSR* v. *Teleflex* (*16*), in which the court changed the longstanding interpretation of the statutory requirements to prove nonobviousness of an invention. This case has been perceived by some as weakening patent protection by holding an invention unpatentable if there are a finite number of identified predictable alternatives that would

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be obvious to try. The prior law had emphasized that obviousness required a reasonable expectation of success (*17*). The case also, for the first time, sanctioned the combination of references from unrelated fields to prove obviousness (*18*) and held that "ordinary creativity" may not qualify for patent protection. In this way some have argued that the bar for patentability was raised without the type of public debate and stakeholder voice that occurs during the consideration of a new law in Congress. Also, it applied retroactively. Some research programs funded by biologic or pharmaceutical companies in reasonable reliance on the old law were suddenly at risk of no patent protection, with a potential wasting of employee time and resources (*19*).

In the case of *In re Bilski* (*20*, *21*), the Supreme Court is reconsidering how to interpret the statute covering what constitutes patentable subject matter (*22*). At what point does an idea pass from an abstract theory to a patentable invention? Relevant to the pharmaceutical industry could be the patentability of medical diagnostic methods, assays, and the use of biomarkers (*23*).

In *Ariad* v. *Lilly*, the U.S. Court of Appeals for the Federal Circuit (CAFC), is reconsidering how to interpret a statute that defines how much and what kind of patent disclosure is necessary to provide an adequate description of an invention (*24*–*26*). This statute, with wording that has not changed in 57 years, could thereafter be reconsidered by the U.S. Supreme Court. Is it sufficient that a patent applicant teach how to obtain an innovation, or must the applicant go further and actually provide sufficient detail on what the invention is, such as physical characteristics of the innovation itself, to establish that the applicant had possession of the invention at the time of filing? For example, is it sufficient to teach how to obtain a new pharmaceutical drug, gene, or protein, or must one describe exactly what the new drug, gene, or protein is?

Retroactive judicial decisions can have several effects. They can facilitate the increase of challenges by generic producers under Hatch-Waxman, which compresses the pay-back period for drugs. They can stop R&D investment decisions that have already been made and could prevent a product from reaching the market because of patentability issues. They can also potentially prevent some R&D from taking place to begin with.

An issued patent is property just like a piece of land or a house (*27*, *28*). When a federal judicial decision dramatically changes the law, such that a valid patent becomes invalid, has the federal government taken private property in violation of the federal Constitution? Application of the Fifth Amendment is not clearly limited to legislative and executive action; nothing in its text bars extension of the takings clause to judicial action. This question continues to be debated (*29*, *30*).

Conclusion

The time has come to rethink the right legal framework to promote and protect investment in pharmaceutical research and development. The Hatch-Waxman Act should be amended to increase the period of R&D data exclusivity from 5 to 14 years (consistent with the current patent term cap) (*31*). This should substantially increase the number of drugs in the R&D pipeline, which could greatly benefit patients and ultimately benefit generic companies. The act should also be amended to allow at least one patent term on the drug to begin on FDA approval. In this way, the innovator is not penalized for the lengthy federal regulatory review process. In addition, to provide an environment that supports long-term good faith business decisions and protect justified prior reliance by innovators, Congress should pass a law that gives an appellate court discretion to mark a decision for prospective application only, if it overrules a prior interpretation of patent statutory law.

References and Notes

1. J. A. DiMasi, H. G. Grabowski, *Manag. Decis. Econ.* **28**, 469 (2007).
2. J. A. DiMasi, *Pharmacoeconomics* **20** (Suppl 3), 1 (2002).
3. J. A. DiMasi, R. W. Hansen, H. G. Grabowski, *J. Health Econ.* **22**, 151 (2003).
4. J. A. DiMasi, R. W. Hansen, H. G. Grabowski, L. Lasagna, *J. Health Econ.* **10**, 107 (1991).
5. The Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S. Code (U.S.C.) § 355.
6. 21 U.S.C. § 355(c)(3)(E)(ii).
7. This 5-year term is often referred to as a "data exclusivity period" but may be considered a forced data-sharing requirement.
8. M. J. Higgins, S. J. Graham, *Science* **326**, 370 (2009).
9. If a generic company files an abbreviated new drug application during the 5-year period and certifies that a listed innovator patent is invalid or not infringed, the FDA will stay approval of the generic drug for 30 months during patent litigation, up to a cap of 7.5 years. See (*32*).
10. The cost to generic companies of demonstrating bioequivalence typically pales in comparison to the cost to innovator companies of collecting preclinical and clinical safety and efficacy data.
11. U.S. Const. amend. V.
12. In *Ruckelshaus* v. *Monsanto Company* (*33*), the U.S. Supreme Court held that a federal law that allows companies to rely on innovator pesticide data to get approval for a generic version 10 years after first approval is not a taking of property, as Monsanto was aware of the law when it submitted its innovator data for pesticide approval. However, in the post-Monsanto case of *Palazzolo* v. *Rhode Island* (*34*), the Supreme Court held that takings claims cannot be defeated merely because the legislature has amended a statute to give prospective notice of some new limitation on property. Hence, Hatch-Waxman is not insulated from takings claims involving patents issued after that statute was passed, and the economic impact of the outdated law supports compensation.
13. Contents and term of patent; provisional rights, 35 U.S.C. § 154.
14. As one example, U.S. Patent No. 6,637,447 covering the "Beerella" an umbrella that snaps onto a beer bottle has 18 years of useful patent life, whereas U.S. Patent No. 6,713,485 on a metastatic breast cancer therapy has 13.5 years of useful life.
15. If a court makes a ruling prospective only, it appears to cross the line into the policy-making function reserved for the political branches. See (*35*).
16. *KSR Int'l Co.* v. *Teleflex, Inc.*, 550 U.S. 398 (2007).
17. *Amgen* v. *Chugai Pharmaceuticals Co.*, 927 F. 2d 1200, 1208–1209 (Fed. Cir.), cert. denied 502 U.S. 856 (1999).
18. In so holding, the Supreme Court overruled the prior "teaching, suggesting, motivation" test for obviousness that required that a reference itself contain the motivation to combine it with a second reference (*36*).
19. In the mid-1990s, the CAFC issued the landmark decisions of *In re Deuel* (*37*), and *Regents of the Univ. of Cal.* v. *Eli Lilly & Co.* (*38*). *Deuel* ruled that "knowledge of a protein does not give one a conception of a particular DNA encoding it." In the Lilly case, the court held that one cannot obtain a patent on cDNA simply by providing a probe and explaining how to use the probe to isolate cDNA, even if the protein encoded by the cDNA is known. Rather, the applicant must disclose the sequence of the DNA to get a claim to the DNA. Years later, the CAFC was compelled to overrule *Deuel* because the Supreme Court referred to that case with disfavor in its 2007 KSR opinion (*16*). The court held that a gene was not patentable to Amgen because its protein was known, even though the patent application was filed only 3 years after the *Deuel* decision. See (*39*).
20. 545 F.3d 943 (Fed. Cir 2008); cert granted 556 U.S. 1 (1 June 2009).
21. The oral argument was heard 9 November 2009, with a written decision expected soon.
22. 35 U.S.C. § 101.
23. *Bilski* pertains to a method for hedging risk in commodity trading. The decision being appealed holds that an innovation is patentable only if it involves a "machine or transformation."
24. 35 U.S.C. §112.
25. Ariad Pharms., *Inc.* v. *Eli Lilly & Co.*, 560 F.3d 1366 (Fed. Cir. 2009); U.S. Patent No. 6,410,516 (filed 5 June 1995); *Ariad Pharms., Inc.* v. *Eli Lilly & Co.*, No. 2008-1248, 2009 WL 2573004 (Fed. Cir. 21 August 2009).
26. CAFC heard full-court oral argument in *Ariad* v. *Lilly* on 7 December 2009, with a decision due shortly. See also (*40*).
27. *Consolidated Fruit-Jar Co.* v. *Wright*, 84 U.S. 92, 96 (1876).
28. *Patlex Corp*. v. *Mossinghoff*, 758 F.2d 594, 599 (Fed. Cir. 1985).
29. J. N. Bunch, *Tex. Law Rev.* **83**, 1747 (2005).
30. D. R. Cahoy, . *Am. Bus. Law. J.* **41**, 1 (2003).
31. The current congressional debate about whether to impose a data exclusivity requirement for follow on biologics focuses on 12 to 14.5 years. S. 1695 and H. 1548.
32. 21 U.S.C. § 355 (j)(5)(B)(iii).
33. *Ruckelshaus* v. *Monsanto Company*, 467 U.S. 986; 1005 (1984) [citing (*41*)].
34. *Palazollo* v. *Rhode Island*, 533 U.S. 606, 626–630 (2001).
35. *Harper* v. *Va. Dep't of Taxation*, 509 U.S. 86, 97 (1993).
36. *In re Grabiak*, 769 F. 2d 729 (Fed. Cir. 1985).
37. *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).
38. *Regents of the Univ. of Cal.* v. *Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997).
39. *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009).
40. Brief for GlaxoSmithKline as Amicus Curiae Supporting Defendant-Appellant Eli Lilly & Company, No. 2008-1248 (Fed. Cir. 19 November 2009) (en banc).
41. *PruneYard Shopping Ctr.* v. *Robins*, 447 U.S. 74, 83 (1980).

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