Will pharmacogenomics alter the role of patents in drug development?

Rebecca S Eisenberg

University of Michigan Law School, 625 S. State St., Ann Arbor, Michigan 48109, USA
Tel: +1 734 763 1372;
Fax: +1 734 763 9375;
E-mail: rse@umich.edu

'Many institutions are scrambling to stake out strong patent positions on advances in pharmacogenomics.'

The field of pharmacogenomics promises to bring considerable value to a commercial marketplace in which patents really matter. Biopharmaceutical research has long stood out as a shining success story for the patent system in motivating private investment in research and development (R&D), consistently outranking other industries both in avowed patent-sensitivity of firms [1] and R&D expenditures [101]. While insurers and governments have struggled to control rising expenditures on drugs, the market has continued to show a strong demand for new products emerging from pharmaceutical R&D.

Pharmacogenomics can enhance the value of these products by predicting differences among patients in the efficacy and toxicity of drugs, thereby minimizing risks. Patients should be willing to pay more for drugs that have been preselected to work well for them than they now pay for drugs that might have no benefits or toxic side effects. In the complex and changing economic and political environment for healthcare, however, it remains unclear who will capture that value. The benefits might ultimately accrue primarily to insurers and government payors, developers of pharmacogenomic diagnostic products, and patients, while drug developers adapt to smaller markets for each new product.

Advances in pharmacogenomics nonetheless offer unequivocal benefits to pharmaceutical firms to the extent that they accelerate new drug development. Pharmacogenomics provides powerful tools for understanding biochemical pathways and mechanisms involved in disease and drug disposition. These tools could bring new products into view or exclude at an early stage products that might otherwise consume considerable time and expense before ultimately failing in the clinic. Pharmacogenomic tests could also help to speed new drugs past regulatory hurdles by permitting the stratification of subpopulations of patients in clinical trials. Drugs that show an unacceptable balance of safety and efficacy when administered to an undifferentiated sample of patients with the same disease phenotype might appear relatively safe and effective in trials that exclude non-responders or non-metabolizers on the basis of genotype.

Many institutions are scrambling to stake out strong patent positions on advances in pharmacogenomics [102]. Given the longstanding importance of patents to the biopharmaceutical industry, and given the likely future importance of pharmacogenomics to biopharmaceutical R&D, one might expect to see an interesting story unfolding about patents and pharmacogenomics and drug development. It is not yet clear, however, just what that story is.

A tantalizing hint that the advent of pharmacogenomics heralds something other than business as usual in the nexus between patents and product development is the position of the SNP Consortium on patents [103]. The SNP Consortium is composed primarily of pharmaceutical firms, a group known for ardent advocacy of strong patent protection throughout the world. Yet when they get together to fund SNP identification, the same firms proclaim a collective strategy of putting information into the public domain as quickly as possible. That these champions of the patent system should join forces to forestall patent protection on SNPs suggests that the distribution of payoffs from patents on pharmacogenomic discoveries is likely to be quite different than the distribution of payoffs from patents on drugs.

'There are limits to the foresight and control of firms over how this technology will unfold and where its commercial benefits will fall.'

The SNP Consortium website [103] highlights one important difference between SNP discovery and drug discovery: from the perspective of the pharmaceutical industry, SNP discovery is 'precompetitive' R&D that builds a platform for future product development. Rather than hoarding SNPs within firms as a proprietary resource, which would likely lead to duplication of effort, Consortium members might expect to make more

Ashley Publications Ltd
www.ashley-pub.com

 ISSN 1462-2416

money sooner if they initially cooperate to accelerate progress in fundamental research. They can then compete later on to develop new products out of the bounty of future knowledge that results.

The virtues of a precompetitive public domain are particularly plausible for a resource like SNPs that becomes more valuable when assembled in aggregations. More SNPs can be used to build more complete maps or informative pharmacogenomic tests, but if different players hold patent rights on different markers, it could prove difficult or costly to assemble the necessary licenses. By joining together to put markers in the public domain, each firm minimizes the risk that it will have to pay hold-up prices for future licenses to use the markers it needs, while still retaining the option of patenting particular products that cull the most informative markers for a particular purpose from the larger set in the public domain.

Another, more cynical account of the motivations of the pharmaceutical industry with respect to pharmacogenomics was suggested by a story that ran in the Wall Street Journal last summer under the headline 'Big Drug Makers Try to Postpone Custom Regimens' [2]. According to this account, pharmacogenomic testing "threatens to be so disruptive to the business of big drug companies – it could limit the market for some of their blockbuster products – that many of them are resisting its widespread use."

According to some estimates, as few as one-third of patients actually benefit from the drugs that are currently prescribed for them. Firms that sell these products would have little incentive to develop tests that alert two-thirds of their current customers to the fact that they are wasting their money. Faced with the prospect of losing significant sales volume, firms might use patents to suppress the introduction of pharmacogenomic tests that identify non-responders to their approved products. It does not necessarily follow, however, that the pharmaceutical industry would seek to suppress progress in pharmacogenomics more broadly, particularly insofar as it facilitates the development and regulatory approval of new products. Firms would presumably welcome the development of pharmacogenomic tests that identify patients who suffer serious side effects from their products, both to limit harm (with the potential for resulting tort liability or withdrawal of products from the market) and to exclude these patients from clinical trials.

'Firms that hope to continue profiting from drug development will want to retain as much control as possible over how pharmacogenomics is used.'

If pharmaceutical firms enjoyed perfect foresight and control over the development and deployment of pharmacogenomic tests, they might choose to pursue those applications that help them bring more products to market (or bring products to market more cheaply), while neglecting those that could steer consumers away from products that are harmless but ineffective for them. It might seem to follow that the pharmaceutical industry should display a greater interest in investigating genetic differences in enzymes involved in drug metabolism, for example, than in investigating genetic differences in drug targets. But understanding pharmacodynamic differences between responders and non-responders to candidate drugs might suggest new targets for pharmaceutical products, and the exclusion of non-responders from clinical trials might improve the balance of safety and efficacy for products under development. There are limits to the foresight and control of firms over how this technology will unfold and where its commercial benefits will fall.

Given these uncertainties, firms that hope to continue profiting from drug development will want to retain as much control as possible over how pharmacogenomics is used. It is thus not surprising that pharmaceutical firms are filing for patents on tests to predict patient responses to their drugs, nor is it inconsistent with the intellectual property strategy of the SNP Consortium. The SNP Consortium, in contrast to the Free Software Movement, is not an unbridled champion of the public domain. It is a limited effort to create a non-proprietary resource for use in upstream R&D, driven by the long-term goal of accelerating the development of proprietary products free of patent claims from research rivals.

If firms hope to use pharmacogenomic markers to gain regulatory approval to sell drugs that are safe and effective in some patients but dangerous or ineffective in others, an additional legal factor that could complicate the role of patents is drug regulation. The need to secure US Food and Drug Administration (FDA) approval in order to sell drugs is both a costly regulatory burden and a

significant entry barrier that operates in tandem with patents to limit competition in the market for drugs. Although the definition of 'drug' in the US Food, Drug and Cosmetic Act includes diagnostic products [3], so far the FDA has focused its resources primarily on regulating therapeutic products. Firms must submit data from clinical trials to establish both the safety and efficacy of new drugs in order to secure FDA approval to bring their products to market. These clinical trials are limited to patients that meet strict entry criteria, and FDA approval is limited to the indications for which the data indicate that the product is safe and effective. These limitations are incorporated in the required label for the drug, and FDA regulations prohibit firms from explicitly marketing drugs for uses that the agency has not approved [4]. But FDA does not regulate the practice of medicine, and pharmaceutical firms typically earn a significant portion of their profits from sales to patients whose physicians have prescribed approved products for a broader range of unapproved, 'off-label' uses. The combination of strict regulatory standards for new drug approvals, and far more limited regulation of off-label uses, often makes it advantageous to design clinical trials for the FDA around relatively narrow indications, in the expectation that the post-approval market for the product will be considerably broader.

'The law may at some point require coordinated development and marketing of a pharmacogenomic test along with the therapeutic product.'

Pharmacogenomics has the potential to alter this regulatory balance. If the determination that a drug is safe and effective depends critically on patient genotype, the law may at some point require coordinated development and marketing of a pharmacogenomic test along with the therapeutic product. The FDA could require administration of such a test in the label for a new drug, or perhaps require the submission of clinical data to establish the validity of such a test before approving the drug for an indicated patient subpopulation, or even require a separate new drug application for the test product [5].

Although the FDA may lack the regulatory authority to limit the prescriptions that physicians write for a new drug according to patient genotype, it might legitimately take into account the likely prescribing behavior of physicians in deciding whether to approve a drug that presents significant hazards if administered to an unscreened patient population. Depending on costs, insurers might conceivably require the use of pharmacogenomic tests before they will pay for certain new drugs, and ultimately, fear of tort liability might accelerate the adoption of pharmacogenomic tests to prevent toxic side effects.

One possible result could be a reallocation of the value of patent rights between therapeutic and diagnostic products. As a practical matter, it may be easier to extract high profits from the sale of therapeutic products to treat chronic diseases over an extended period of time than it is to extract profits from sales of diagnostic tests to the same patient population on a one-time basis. Payors may balk at paying high prices upfront for diagnostic tests. On the other hand, owners of patented diagnostic products would hold considerable leverage in negotiating with firms that could not lawfully market new therapeutic products without them, and might use their leverage to secure a promise of royalties on future product sales.

If pharmacogenomics fulfills its promise of predicting patient reactions to drugs, many factors will converge to create strong demand for this technology. Patients will want to know what drugs will work best for them, payors will want to spare the expense of buying drugs that do not benefit particular patients, drug developers will want to bring to market products that would otherwise fail regulatory tests for safety and efficacy, and regulators will want to ensure that approved products are administered appropriately. In order to secure these benefits, it may prove necessary to coordinate the development and marketing of new drugs with pharmacogenomic diagnostic products. In anticipation of this development, many institutions are seeking patent claims on advances in pharmacogenomics that they hope will permit them to share the wealth from future products. The bargaining positions of the parties may depend on the strength of their patent positions.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Cohen WM, Nelson RR, Walsh JP: Protecting their intellectual assets: appropriability conditions and why US manufacturing firms patent (or not). NBER Working Paper No. 7552. Nat'l Bureau of Econ. Res. Cambridge, MA, USA (2000).
2. Anand G: Big drug makers try to postpone custom regimens. *Wall Street Journal*, June 18 (2001).
3. 21 US Code § 321(g)(1)(B).

• Provides what the term 'drug' means: 'Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.'

4. Washington Legal Foundation v. Friedman, 13 F. Supp.2d 51 D.D.C. (1998).

•• The First Amendment is emerging as a constraint on the power of FDA to restrict the marketing activities of pharmaceutical firms in the US.

5. Lesko LJ, Woodcock J: Pharmacogenomic-guided drug development: regulatory perspective. *Pharmacogenomics J.* 2, 20-24 (2002).

•• An interesting analysis of the regulatory implications on pharmacogenomic-guided drug development.

Websites

101. www.phrma.org/publications/publications/profile01/chapter2.phtml
Pharmaceutical Research and Manufacturers of American, Pharmaceutical Industrial Profile 2001, Fig. 2-3, citing data from PhRMA and Standard & Poor's Compustat).
102. www.pharmacogenomicsonline.com/publications/patents.html
Abstracts for some of these patents and patent applications are found at this address.
103. http://snp.cshl.org/about/program.shtml
SNP Consortium website, last visited August 7, 2002.