Patent Prosecution in Pharmacogenomics

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Abstract

This paper presents a brief overview of intellectual property rights and the various areas in pharmacogenomics to which IP rights may be applicable. Technology transfer, including licensing and business agreements, is not covered in this paper. Instead, issues and complications related to national and overseas patent prosecution in this relatively new field will be discussed.

Intellectual Property Overview

Some find the concept of intellectual property hard to grasp, often because it's hard to determine the monetary worth of ideas. One simple example of the value of intellectual property is the common occurrence of expensive and high-stakes infringement lawsuits. One of the costliest examples is the decades long case of Eastman Kodak vs. Polaroid, which resulted in the destruction of Kodak's instant photography business, as well as more than $3 billion dollars in infringement damages, compensation and legal fees, and research and manufacturing costs (1). Even lawsuits that result in settlements, such as that filed by the University of California against Genentech for the company's manufacture and sale of the growth hormone product Protropin^{R}, can be severe ($200 million in the case of UC vs. Genentech) punishments for the defendants (2). That is not to mention the hundreds of thousands of dollars lost by both sides on legal and courtroom fees and on time spent by employees and management embroiled in the suit.

Although successful suits filed by small companies can result in large settlements or infringement damages from industry juggernauts, companies without the proverbial 'deep pockets' typically do not have the time and money to spend on lengthy, costly litigation. The price of resolving patent disputes can sometimes cripple a business, compared with the modest cost of building an effective IP portfolio. Thus, successful companies stand to benefit more from a strong IP portfolio to accompany equally strong and innovative research and development. Besides, with sound and successful innovation, a company can avoid being mired in litigation over a technology that it has long since improved upon.

From a different angle, those still questioning the value of intellectual property can look at the value derived from successful licensing of IP. The well-known Cohen-Boyer recombinant DNA patents, often credited as key catalysts of today's biotech industry, were reported to have earned $37.3 million in licensing royalties in 1997 alone (3).

While U.S. legislation such as the Bayh-Dole Act allowed for transfer of ownership of many government funded inventions from the U.S. government to the universities (4), resulting in successful licensing of almost half of university-born inventions (5) (6), the fact is that an estimated 3% of all patents are actually licensed (7). Thus an effective IP prosecution strategy should take note of the competing demands for licensing revenue and defense from litigious competitors. On one hand well-written patents are needed to defend the core technologies a company builds upon, and on the other hand an aggressive patenting strategy is needed to map the course a company sees itself undertaking. The latter can result in licensing deals, or serve as a useful method for sidestepping unwanted litigation, by keeping far ahead of the competition.

This paper presents a brief overview of intellectual property rights and the various areas in pharmacogenomics to which IP rights may be applicable. The perfection of an IP portfolio is of interest to startups and their investors, whereas licensing agreements are of interest to manufacturers and customers. Technology transfer, including licensing and business agreements, is not covered in this paper. Instead, issues and complications related to national and overseas patent prosecution in this relatively new field will be discussed.

Patents

United States patents offer protection for any process, machine, manufacture, or composition of matter, or any improvement thereof, that are novel, useful, and non-obvious (8). The Agreement in Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreements) in 1994, a multilateral concord proposed by the council administering the WTO's intellectual property agreement (9), defines patentable matter as any invention that involves an innovative step and has a potential industrial application (10).

In theory, the purpose of intellectual property is to foster intellectual and economic growth. Patents spur innovation through the disclosure and teaching of the details of an invention to the public, and in exchange, the inventor or owner is rewarded the legal rights of ownership. The legal rights give the owner exclusive rights to capitalize on the invention, by excluding others from making or using the invention, importing the invention into the U.S., or offering the invention for sale. These ownership rights are granted for a period of 17-20 years, depending on the date of filing of the patent.

Patents are obtained through a lengthy process that can sometimes turn out to be quite costly. In high-tech fields such as pharmacogenomics, the time between filing a patent and a first response from the U.S. patent office is typically a year and a half. This is due in part to the large volume of patent applications in these fields, and to the lack of expertise in the patent examiner corps. In Europe, Japan, and the Pacific, the "first to file" system applies. On the other hand, in the U.S. the "first-to-invent" system applies, but patent applications must be filed within one year of the first offer for sale of the product or the patent filing will be void. Thus it is important to keep an accurate record of dates of invention as well as offers for sale or other public disclosures.

Copyrights

Copyrights protect the original expression of an idea. By offering protection, copyright encourages the expression of original, artistic ideas into a tangible medium. Legal protection is effected instantly, when the original copyrightable subject matter is fixed into a tangible medium, e.g. on paper or in a digital storage form.

Copyrights are free and do not require months of paperwork as do patents, and they are valid for the author's lifetime plus 50 years. A longer period of validity (75-100 years) applies if the work was created for hire, which is generally the case in a business such as the biotech industry.

Trade Secrets

Trade secrets are any technical or business information that give a company a competitive advantage. There is no formal filing procedure to register trade secrets. The secret need not be completely novel or exclusive; it simply must have a derived or potential economic value from being unknown. Additionally, reasonable efforts must be made to keep the information secret, e.g. through the inexpensive use of Non-Disclosure Agreements (NDA). Legal protection under trade secret no longer applies when the information is publicly disseminated.

Trademarks

Trademarks refer to the distinctive signature mark that can be used to protect the company, product, service, name, or symbol. The trademark must not be descriptive or generic. Legal protection is not offered to the technology, rather to the company good will and quality associated with the use of the recognized name or symbol. Trademarks provide exclusive rights within a region or nation and as long as used commercially, and they may be renewed indefinitely. Compared to patents, they are obtained within a moderate time period (usually under two years) and typically at a cost under $5K per registered mark.

IP Strategy

The IP rights are protected under various federal and state laws. Without protection, intellectual property falls into the public domain and may be used by any party without license. A sound management strategy would be to systematically build a portfolio consisting of different IP rights, with the aim of protecting the various aspects of the company's technology and commercial interests.

IP rights protect the commercial interests of a company at the various stages of design, manufacturing, and product operation. At the design and development stage, copyrights and trade secrets can be immediately enforced. Novel apparatus and methods can then be patented, a process that takes

about three years and requires the investment of some funds. Once a product or service is developed, issued patents and trademarks protect the technology and associated names and symbols.

While copyright and trade secret protection are obtained easily, patents, trademarks, and maskworks require applicant action and response within critical filing deadlines. Generally, the first to patent will have the best chance of winning the broadest patents.

Pharmacogenomics

Pharmacogenomics stems from a related field, pharmacogenetics, and the two terms are often used interchangeably. Pharmacogenetics is the decades-old study of differences in drug absorption, metabolism, elimination or response and then examines a few candidate genes for variations underlying the observed phenotypes. In contrast, pharmacogenomics casts a wider net to capture complicated patterns of genetic variation and attempts to correlate these patterns to different drug response phenotypes (11). The challenge is to identify genetic differences that influence drug metabolism and response, and to correlate that data with drug efficacy and safety information. The goal is to weave all this information together into something that has enough predictive value to be used reliably.

Single nucleotide polymorphisms (SNPs pronounced "snips") are the most prevalent genetic variations in the human genome. They are single base pair differences that occur in 1% of the human population (13) on average every 1.91 kb. The human SNP map shows1.42 million differences, a majority of which occur in coding regions (12). Pharmacogenomics is the study of how these sequence differences affects the ways in which people respond to drugs. Variations in the disease-causing genes, drug targets or the enzymes that metabolize drugs influence the drug's potency and efficacy. Also, genetic differences between patients explain why some patients but not others suffer from harmful drug side effects.

Challenges

Currently, costs limit the widespread use of pharmacogenomics. For instance, it costs approximately one dollar to identify one SNP in a patient sample (13). It is estimated that it will require the screening of 100,000 SNPs per patient to construct an accurate picture of a patient's response to a drug; this translates to 100,000 dollars per patient. For this technology to become practicable, the cost must be reduced to a penny per SNP. Further, narrowing down a large number of genetic variations to a number that is amenable to application in a clinical trial would also prove useful. In this regard, computation methods to categorize and prioritize SNPs or haplotyping, the identification of closely associated polymorphisms that tend to occur in clusters, are being developed (11).

Other limitations in the progress of pharmacogenomics include tools used for collecting, archiving, organizing and interpreting the huge amount of data generated in a pharmacogenomics study so that data from diverse experiments can be compared. Also, drug dosage and treatment schedules need to be standardized in order to accurately compare patient data (11). Successful interpretation of data also requires comparison of enormous quantities of data such as the publicly available databases, Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) and the SNP Consortium (14).

Uses

The primary goal of pharmacogenomics is to reduce the time and cost of drug development. Choosing patient candidates for a clinical trial based on pharmacogenomic knowledge and the patients' genotype is hoped to eliminate sub-populations for whom drugs are predicted to be ineffective. This would justify smaller and fewer trials, likely generate more consistent trial results, and make it easier to gain FDA approval (15).

Another goal of pharmacogenomics is to identify patients who are likely to suffer drug related adverse events. A 1998 study of hospitalized patients published in the Journal of the American Medical Association reported that in 1994, there were more than 2.2 million adverse drug reactions and 100,000 drug-related deaths, making adverse drug reactions one of the leading causes of hospitalization and death in the United States. Moreover, the ability to pre-test patients may have prevented certain high profile drug withdrawals, including the former Warner-Lambert Rezulin (troglitazone) and Glaxo Wellcome's Lotronex (alosetron) (15).

Pharmacogenomics can be used to identify how quickly a patient will metabolize a drug and, therefore, ensure appropriate dosing. Up to 30% patients do not respond optimally to certain drugs, this can often be addressed by merely changing the dose. If these problems were identified and remedied early in

clinical trials, results would be more convincing and, therefore, approval would be faster and less costly (15).

Pharmacogenomics will allow the differentiation of a company's product from others in the marketplace (e.g. by identifying patient's by genotype who will respond to product X and not to product Y). One further benefit to patients is that pharmacogenomic knowledge will also allow identification of those patients in the population who will derive no clinical benefit from a prospective treatment. A look at data from clinical trials in 14 major drug categories reveals that this "non-responder" subset may be 20-75% of the general population. Additionally, pharmacogenomic knowledge from association studies (SNP to disease links) will allow for preventative screening and preventative treatment.

Drug patent holders in pharmaceutical industry have many incentives to use pharmacogenomic knowledge to develop genotyping diagnostic tests to be used with a drug. They have a vested interest in having shorter, less expensive clinical trials, identifying patients who are expected to have adverse drug reactions and those requiring tailored dosages of drug. However, the anticipated loss of sales revenue by identification of the "non-responders" serves as a strict disincentive for the development of genotyping diagnostic tests.

Protectable Applications in Pharmacogenomics

Tools

The tools available to researchers involved in pharmacogenomics studies are viewed as patentable. These include reagents, kits, chips, microarrays, instrumentation, devices used for genetic tests, algorithms for searching and sequence alignments and database technology. Certain proteins may also fall under the tool category if they can be used as probes to identify other biomolecules or small molecules

Composition

The composition of isolated nucleic acid sequence, isolated protein and small molecules can be claimed. A patent application has to comply with the requirements for utility, novelty and non-obviousness. Further, the patent application must also comply with requirements for written description, enablement and best mode. For example, one has not shown utility if one claims a nucleic acid sequence that may be used as a gene probe, a primer in PCR, a chromosome marker or an antigen generator since such utility is applicable to virtually any nucleic acid sequence. However, if the function of the gene is known and its utility is understood then claiming the DNA, as a gene probe, would be valid. Further, if the gene function is known and the utility is accepted then a homologous DNA sequence would comply with the utility requirements and could be claimed. Even if a portion of this homologous gene was previously published as an expressed sequence tag (EST), the patenting of this homologous gene still complies with the novelty requirement. While a single nucleotide polymorphism or a nucleic acid sequence containing such a variation can not be claimed, if such a variation proved useful as a marker for a disease state or for drug metabolism, the composition could be claimed. The written description requirement is the greatest hurdle for patenting of composition in inventions. In an age where "describing a method of preparing a cDNA or even describing the protein that the cDNA encodes. …does not necessarily describe the cDNA itself" one can be sure that the written description requirement is very strictly enforced (16).

Methods

Patenting methods that aid in the acquisition of pharmacogenomic data such as screening and genotyping methods is standard practice. Further, methods used in the diagnosis and treatment of subjects based on pharmacogenomic knowledge are also patentable. Interestingly, methods for management of complex data from pharmacogenomic studies such as a method for integrating clinical, diagnostic, genomic and therapeutic data is patentable. Finally, methods for pharmacogenomics-based clinical trial design meet the criteria for patentability.

Challenges to Patent Process in Pharmacogenomics

As already touched upon, there exist some challenges that are specific to the pharmacogenomics patent process. The main issues for obtaining commercially relevant patent protection in

pharmacogenomics are utility, enablement and written description. However, the challenges in enforcing pharmacogenomics patents may prove to be the larger problem in the patent process.

Groups involved in developing pharmacogenomic research tools and methods should be aware of the *Housey* decision passed by the district court of Delaware. In accordance with this decision the one can elude US protection on patented screening methods by performing the research work outside the United States. Once the screening is completed and a useful product is found, the *Housey* decision permits the information to be brought back into the United States for further testing and development into a commercial product (16).

The research exemption is designed to protect actions performed "for amusement, to satisfy idle curiosity, and for strictly philosophical inquiry". As seen in the case of *Madey vs. Duke University* the experimental use defense is not valid if the activity furthered the "legitimate business objectives" of the alleged infringer whether or not a profit was made. This defense is "very narrow and strictly limited" (16).

The exemption to infringement under 35 USC 271 (e)(1) provides that it is not an act of infringement to use a patented invention solely for uses "reasonably related" to the generation of information likely to be relevant to FDA approval of a product. This exemption may be applied in the case of business methods, devices, research tool and even chemical entities. Unlike the research exemption, this exemption has been interpreted broadly and judged as non-infringement in favor of the defendant in the *Bristol-Meyers Squibb vs. Rhone-Poulenc Rorer* case (16). The scope of the 35 USC exceptions was reigned in by an opinion from the Court of Appeals for the Federal Circuit in the case of *Integra vs. Merck.* In this case the use of patented research tool in drug discovery was deemed as infringement as pre-clinical work is not included in the safe harbor of 35 USC 271 (e)(1) (17).

The EPO also has specific laws pertaining to biotechnology patents, described in the EU Biotechnology Directive of July 1998, and the European Patent Convention (EPC) of 1999. For instance, Article 53(a) of the EPC states that "European patents shall not be granted in respect of… inventions the publication or exploitation of which would be contrary to 'ordre public' or morality" (18), and Rule 23d(d) excludes "processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes" (19). Thus, patents that cover genetically modified animals, for example, that do not specify or imply medical benefits can be rejected by the EPO or challenged in an Opposition, a procedure in which any person may oppose a granted European patent within nine months from publication.

Finally, the notable rule pertaining specifically to biotechnology patents in both the US and Europe is that of utility. Under amended guidelines issued in January 2001, patentable subject matter is that which has specific, substantial, and credible utility. The addition of the substantiality requirement means that patent claims that require considerable research by a person of ordinary skill in the art in order to determine the function of a molecule are likely to be rejected. The motivation for the requirement is to reduce claims that expands the scope of the invention beyond the functions and utility described in the specifications. In its most simplified interpretation, the utility rule demands that each claim pertain to products that have a clear use and benefit to human society.

The challenges to pharmacogenomics patents are still evolving. Because of their direct application to biological life on earth, pharmacogenomics and genomics patents are subject to intense scrutiny by the various patent offices. As the technology develops, however, one impedance to the biotech patent process, namely the need for more cross-technically educated patent examiners and counsel, will eventually become less of a burden. Knowledge of the challenges to the pharmacogenomics patent process will lead to more skillful prosecution and more rapid innovation overall.

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