
PATENTS ARE NOT TRIVIAL: THE CASE FOR INNOVATION IN RESEARCH AND DEVELOPMENT WITHIN THE BIOMEDICAL INDUSTRY

One of the key arguments against R&D within the biomedical industry is that it focuses substantial resources on developing marginal improvements to existing therapies. Also, because the objective is to extend the commercial life of current products, the patient does not benefit from a true medical advance. It is alleged that the current patent system supports this strategy by allowing the industry to claim patent protection for a host of trivial or minor changes—often shortly before the original patent expires—in order to extend the period of exclusivity and prevent commercial rivals from entering the market at lower prices. The perceived effect is to restrict generic competition, limit the access of medicines access to the poor and divert resources from research that addresses the disease burden of neglected populations in developing countries.

This article seeks to counter the central premise behind this narrow vision of the R&D industry as both imitative and anti-competitive: that any patent obtained beyond the patent on the original compound itself is “frivolous” because it is motivated solely by commerce rather than a commitment to innovation. In fact, the patent system provides an essential guarantee that inventors will be rewarded for the risks they take in transforming “proof of concept” into a safe and effective medicine, a process that averages more than a decade and consumes enormous financial resources.

What is lost in this debate is the fact that the patent system has stringent requirements that prevent someone from obtaining patent protection for something that is not new. Patent law requires that a patent holder prove that his invention be both novel and “non-obvious”—defined as that which a person with basic skills in the art could not normally derive from prior art, and thus representative of an “inventive step.” In practical terms, this means that the applicant must prove that the invention he seeks to patent has new, improved or unexpected therapeutic effects or properties compared to what is known.

In addition, multiple patents relating to a single product sometimes result because in the product’s development significant hurdles were encountered that if not overcome would have prevented its manufacture or its safe and effective use. Even the most innovative new compound will fail the test of the market if its pharmacokinetic properties prove unstable, if the medicinal content degrades in the human system or cannot be safely stored on the shelf, or if it cannot be manufactured in standardized acceptable quantities, at reasonable cost. These and other “inventive steps” that drive the long journey from laboratory to patient are critical to ensuring that a medicine is approved for the intended indication, with minimal risk to the patient population, and at a cost that the market will bear.

As profiled in a series of concrete examples contained in this paper, an invention can range from manufacturing improvements or modifications to changes in inert or active ingredients. None of these are “trivial” if the end result is a product registered and approved by governments and accepted by patients.

Inventions that assist in successfully overcoming these hurdles are legitimately patentable—from both a patent law and societal benefit perspective. Without them, the product would never have emerged from the registration process intact. Are such facilitating inventions “frivolous” or “trivial”? Not to patients who take the medicine which would not have otherwise been available.

Another point is that a patent covering an improvement to an existing patented product does not bar generic competition against this existing product once the patents protecting that product have expired. For example, if a company develops a once-a-day dose for a product originally prescribed twice daily and patents the new formulation, generic competition is still possible against the original, assuming the patent on the original drug has expired. The only patented protected version will be the new formulation. The market will then decide if the once-a-day benefit is worth a premium over cheaper generic versions of the original product.

The bottom line is simple and unequivocal: multiple patents do not prevent the advent of generic versions of patent-expired products. A product cannot be “double-patented.” A new patent covering an improvement to an existing product protects only the new improved version, such as the once-a-day dosing formulation cited in the example above. Both versions can be on the market; competition is then between the off-patent original product and the patented new version.

Moreover, others can develop and market further formulations or once-a-day versions provided they are different from those covered by the later expiring patent. Only products that offer advantages over the products now free for all to use will be accepted by patients and the medical community. The patent system provides this incentive to “invent around” and thus encourages innovation and effectively precludes the original patentee from extending his exclusive position by making merely trivial changes.

In fact, in our industry, any new product must demonstrate distinct value to the patient and payer communities or it will not be accepted. Physicians, payers or patients do not respond to a new product simply on the basis of its patent status; the level of engagement is far more complex, with assessment of therapeutic benefit driving acceptance by the customer base.

To say that a company can dictate the timing of a patent or series of patents so as to extend a monopoly is simply contrary to the nature of science and the reality of invention. The realization of an inventive step is inherently unpredictable—if it were not, then research and development would not be so resource intensive and time consuming, especially in the pharmaceutical sector. Statistics demonstrate that the first compound in a new class that is patented and submitted for registration is only rarely the first to be actually approved for marketing to consumers. In fact, many compounds are abandoned at some point during the lengthy clinical trial process and never reach patients at all.

INNOVATION: IT'S IN THE EYE OF THE BEHOLDER

There are many types of innovation in pharmaceutical R&D. This question was specifically acknowledged by the European Union [EU] Working Group on Pharmaceuticals and Public Health in its March 2000 report to the EX High Level Committee on Health:

“Innovation in pharmaceuticals encompasses many different options, going from the development of a completely new medicine for the treatment of a disease otherwise incurable, to modifications of known pharmaceutical formulations to improve benefits for the patients, such as a less invasive administration route or a simpler administration schedule.”

The concept of an incremental improvement to an existing pharmaceutical product that can be deemed an innovation worthy of a patent is also recognized and codified in US patent law, as follows:

“Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. “ [35 USC sec.101]

This concept is not limited to the US: it exists and is incorporated in the patent regimes of all countries that have implemented systems that are compliant with the 1994 WTO Agreement on Trade Related Intellectual Property Rights [TRIPS].

Several US government agencies have examined the issue of alleged frivolous patent filing. Of note is the fact that their findings do not support allegations of widespread abuse. A study by the Food and Drug Administration [FDA] found that of the 8,259 generic applications filed in the US between 1984 and January 2001, 94 percent, or 7,781 applications raised no patent issues and involved no patent litigation. Launches of generic products were not impeded by any patents.

The same outcome can be found in a more recent Federal Trade Commission study . The study looked at whether there was abuse by patent holders through the filing of frivolous patent infringement suits as a way to delay the advent of generic competition. Out of the more than 8,000 generic drug applications filed with FDA since 1984, The Commission focused on only eight cases of possible concern. That translates into a finding that about one-tenth of one percent [0.1%] of all generic filings involved possible frivolous patent suits.

Conversely, it can be said that the generic industry itself has a strong incentive for such activity, particularly given the supportive protections offered to the industry under the US Hatch-Waxman Act. Essentially, when a generic company files a generic application (ANDA) with a Paragraph IV Certification (non-infringement or invalid patent), the company is in a minimal risk, maximum reward position. If it wins the case, it gets on the market quickly. If it loses, it owes no damages.

PUTTING THEORY INTO PRACTICE: THREE CASE STUDIES

The following four cases illustrate the value of incremental innovation and the role that patents play in providing a wide range of useful product developments that in turn depend on the time, effort and resources expended by the innovator. These cases demonstrate that patents, far from being a defensive weapon to limit competition among low value products, actually drive technological progress by encouraging and enabling the investment needed to overcome the many hurdles that accompany the long, expensive process of developing a novel idea into a tangible product.

They involve two research-based pharmaceutical companies spanning the past 25 years and have a common theme in that in each case the company:

- Started with a compound that was already patented from a material standpoint (i.e. the chemical form of the compound is protected)
- Faced barriers limiting the compound's benefit for patients, and
- Required further innovative biology/chemistry advances to overcome substantial scientific challenges

The first and most recent case looks at the development of a single dose form of Zithromax, an antibiotic that fights infections. The second case targets the development of a more efficient synthesis process for Neurontin, a drug used for the treatment of neuro-psychiatric disorders. The third examines the development of an extended release form of Procardia, a drug for heart disease and high blood pressure.

CASE STUDY: ZITHROMAX SR [AZITHROMYCIN]

Context

Compliance is a critical issue for patients taking antibiotics to fight infections. Patients who do not complete their prescribed course of therapy are only partially treating the infecting bacteria. This may lead to treatment failure and/or the development of antibiotic resistance. Compliance can be a particularly important issue in resource-poor settings where lack of medical infrastructure can mean low capability to monitor patient progress. Consumer research shows that only about 60 per cent of patients comply with antibiotic therapy.

Compliance can be greatly enhanced by simplifying the treatment regimen such as decreasing the number of tablets taken per day, lessening the overall treatment duration, or by both. While patient compliance is a problem in the developed world, the problem is even greater in the developing world, where healthcare infrastructure is poor. An ideal therapy would require taking the medicine orally, once, at the time of the visit with the physician, sometimes twice per day; however, many drug therapies require taking a large number of doses over as many as fourteen days.

Challenges

Zithromax, an antibiotic used to fight infections, was an improvement over other therapies when it first appeared on the US market because it required a shortened treatment duration of only five days; however, gastro-intestinal (GI) side effects prohibited Zithromax from being taken as a one-time dose for most infections.

About a decade or so ago, Pfizer scientists started a project to turn Zithromax into a single dose form: Zithromax SR. The team faced a series of challenges.

Solution

GI Side Effects: The first step was to understand how Zithromax produced side effects when given in a single dose. Through a series of small scale human studies that spanned two years, Pfizer scientists identified the issue: high concentrations in the upper GI tract produced the side effects, however high concentrations in the lower GI tract did not. The question remained: could they find a way for the drug to bypass the upper GI tract?

Creating a formulation: Pfizer scientists knew that a liquid suspension was the only viable form because a solid form would require patients to take too many pills. During the five year development of the liquid that could deliver the drug to the lower the GI tract, many issues were encountered that required experience and creativity to solve. Two illustrative examples related to how the drug was included in the liquid suspension:

- The scientists created ‘beads’ to carry the drug in the liquid using an innovative composition designed to slow the drug’s release until it reached the lower GI tract;
- They also optimized the size of the ‘beads’ to produce an easily suspended and swallowed liquid suspension, while maintaining the capacity to slowly release the drug.

Optimizing the formulation: Once the liquid suspension was established, it was necessary to determine whether it would actually reduce GI side effects. Before committing to a large Phase III trial, Pfizer performed a Phase II trial in 2001 which failed to show reduced side effects. After a reformulation, Pfizer performed a second Phase II trial in 2002 that was successful.

Testing Efficacy: From 2002-2004 the extended release suspension was successfully tested in over 3000 patients in a Phase III program.

This 13-year process of research and development led to a single dose suspension that met medical and commercial requirements and took significant effort, resources, resilience, and ingenuity. Over 90 full time employee years accompanied by large financial investments were applied to meet this goal. The key achievement of increasing the dose delivered in the single dose to 2g, compared to the previous normal dose of 1.5g delivered over three to five days, was to raise efficacy and further reduce the chance of resistance—i.e. “a dead bug cannot mutate.” The innovative suspension formulation was patented along with the original compound—and was essential to the product’s eventual success. The resulting innovative product has substantial therapeutic value and will have a significant impact in the fight against antibiotic resistance in both the developing and developed world. Zithromax is also now used as the treatment of choice for trachoma, the leading cause of preventable blindness in the developing world.

CASE STUDY: NEURONTIN [GABAPENTIN]

Context

Neurontin is now an important option for the treatment for seizure disorders (epilepsy) and is the leading treatment worldwide for neuropathic pain that can occur after shingles. However, even though safety and therapeutic value were established in Phase I and Phase II clinical trials, the drug was nearly abandoned due to challenges in scaling up the production process to commercial volumes.

Challenges

Warner Lambert faced three key scale-up issues:

- *A very costly process:* Making the drug required extreme physical and chemical conditions, e.g. high temperatures and concentrated acidic solutions. These conditions were very expensive to create, and on a large-scale would result in significant amounts of environmental waste.
- *Limited quantity of drug:* The process was only capable of producing the small quantities of drug adequate for pre-clinical, Phase I and Phase II clinical trials. Regardless of the investment required, it was fundamentally unclear whether the science could be scaled-up to higher volumes.
- *Potential quality issues:* At a small scale, the quality of each individual tablet was high, but if significant increases in scale were achieved, scientists faced further challenges to limit impurities and maintain stability of the drug.

In 1988, ten scientists were given two years to design a more efficient process to reliably produce large quantities of Neurontin. If they could not, the project would be abandoned.

Solution

The nature of invention is essentially unpredictable and many unique problems need to be solved throughout the process. Two examples of challenges faced by the team that required innovations in chemistry were:

- The need to develop an alternative key reagent when the global supply of the reagent used previously was no longer available due to political tensions.
- Designing a reaction that had never been achieved before. This involved academic research, benchmarking across other industries, and developing complex statistical analysis methods to identify the unique conditions and ingredients necessary to produce the desired reaction.

By 1989 the team had invented a novel and efficient process that required less extreme conditions, resulted in little environmental waste, and produced a purer form of Neurontin than the original process. Thereafter, another team of 10 scientists required 2 more years to scale up the new process to the point where it could supply market demand from large manufacturing plants.

This 40 employee-year effort to design a workable production process required significant resources and innovation and was critical to bring this therapy to patients. In recognition of the team's achievements in intellectual property, the new production process was patented in 1992.

CASE STUDY: PROCARDIA XL

Context

Procardia belongs to a class of drugs known as calcium channel blockers (CCBs) and originally came to market in 1982 as a treatment for angina – chest pain associated with coronary heart disease. Today, a number of CCBs are approved for the treatment of high blood pressure (hypertension) and provide significantly greater therapeutic value than when Procardia first came to market. This advance was made possible by addressing issues with the way the original drug was released into the bloodstream.

Challenges

Although capable of relieving angina, the original formulation of Procardia had to be taken three times a day. This regimen was difficult from a patient compliance standpoint and led to large swings in blood levels with accompanying changes in blood pressure that prevented the drug from being completely effective.

Scientists at Pfizer hypothesized that if they could ensure more stable blood levels by creating an extended release form of Procardia, it would have significant potential to change the way the drug was used and benefit a whole new group of patients by treating high blood pressure much more effectively.

Solution

In 1982, Pfizer began a partnership to develop a proprietary extended release technology. Three key issues had to be addressed:

- *Adapting the technology to Procardia:* Since the partner's technology had never been used with a therapeutic, it had to be re-designed specifically for Procardia. This required a two year collaboration between the company and Pfizer scientists to design a system to release Procardia at just the right rate to maintain constant blood levels.
- *Creating mass production facility:* two to three years were then spent developing the equipment to mass produce Procardia XL at a manufacturing site and another year to both build the equipment and gain FDA approval for the production facility.
- *Evaluating clinical activity:* Since this new technology had never reached patients before, the FDA had a number of questions about its reliability. Before Procardia XL could enter Phase II studies, Pfizer ran a wide array of safety studies to address FDA concerns. After answering all of their questions and running successful Phase II and III trials, Procardia XL showed remarkably consistent blood levels over a 24 hour period with fewer side effects than Procardia. Procardia XL was subsequently approved for both angina and high blood pressure indications.

This seven-year process produced a drug that altered the way an entire class of therapeutics was used in patient care. Consistent blood levels of CCBs opened a paradigm of treatment that more than tripled the patient population that could benefit from this therapy. This significant effort and innovation to develop Procardia XL resulted in a patent for the drug formulation.

CASE STUDY: AGENERASE™

Context

Formulation stability and bioavailability is of key importance in the development of a new drug. If it cannot be formulated in a manner in which it can be stored for a suitable length of time, the product will not pass the strict requirements for regulatory approval and thus a potentially valuable new treatment for a disease may never reach the patient. If it cannot be formulated in a manner in which the quantity of the drug needed can be delivered in a dosage form that is acceptable to the patient, then patient compliance problems will arise.

Challenges

Agenerase™ is an HIV protease inhibitor. At the time of its development, protease inhibitors were a relatively new class of drugs for treating HIV. With the HIV virus capable of developing resistance to existing therapies, the medical world was very keen for new therapeutic options for patients.

However, amprenavir, the active substance in Agenerase™, has very low solubility and “wettability” [i.e. the extent to which a solid is wetted by a liquid, measured by the force of adhesion between the two] and was thus very difficult to formulate. In addition, poor solubility resulted in low bioavailability in the powder in capsule and tablet formulations. Bioavailability is a particularly important consideration in the HIV arena since patients generally take a range of treatments and thus have a relatively high pill burden. New treatments with low bioavailability would add to this burden and thus patient compliance would become harder to achieve.

Solution

Scientists at Glaxo SmithKline identified that the bioavailability of amprenavir in conventional capsule or tablet form was low partly due to its high molecular weight [506 g/mol], poor water solubility [0.04 mg/ml, pH 7.5], and high dose [1200 mg twice a day]. They discovered that vitamin E-TPGS [a form of vitamin E that is water soluble, as opposed to other forms which are fat soluble] enhanced the absorption flux of amprenavir and improved its bioavailability. Given the fact that it is relatively safe to use, vitamin E-TPGS was determined to be of high importance to the development of a stable and acceptably bioavailable Agenerase formulation.

The novel and invention solution to the formulation problem, which enabled the product to gain marketing approval and become a viable treatment, was recognized by being granted patent protection. Indeed, without this solution, there would have been no way to ensure the pill was effective for its intended patient population.


 **REFERENCES**

1. Pharmaceuticals and Public Health in the EU: Proposals to the High Level Committee on Health for Policies and Actions in the Framework of the Treaty of Amsterdam, March 2000
2. *See* FTC Generic Drug Entry Prior to Patent Expiration: An FTC Study, July 2002