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Evergreening: A deceptive device in patent rights

Gaurav Dwivedi [1], Sharanabasava Hallihosur [1], Latha Rangan*,[1]

Department of Biotechnology, Indian Institute of Technology, Guwahati, Assam 781 039, India

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A B S T R A C T

Patents are the most important way by which inventors can protect their invention and the income that might derive from innovations developed in return for the full disclosure that enters into public domain after expiration of the patent term. In certain domains, monopolies over patent rights are being extended beyond the patent period, particularly in high-revenue-earning pharmaceutical sectors. This article presents evergreening strategies that are regularly employed by the giant branded pharmaceutical firms as a tactic to bypass existing patent laws and limit generic competition in the marketplace. The article examines the implications of evergreening for different stakeholders, including branded and generic drug companies and consumers. Problems that arise due to evergreening are also discussed. The frequency of such strategies necessitates strong patent interpretations that are protective of the spirit of patent laws.

1. Introduction

A patent, in simple terms, is a temporary monopoly right granted by the government to the inventor for an invention. The system strives to find a balance between reward for innovation and promotion of development by facilitating dissemination of knowledge by disclosure. The temporary period of monopoly gives the inventor a chance to profitably exploit his/her invention and thus provides an incentive for disclosure. This disclosure by itself, promotes further development. Upon expiration of the monopoly period others are free to practice the invention, which again is made easier by the disclosure.

Evergreening, although not a formal legal concept, is a term referring to the numerous ways in which patent owners of pharmaceutical products use the patent laws to extend their monopoly privileges beyond periods that are normally allowed by law, particularly over high-revenue-earning drugs [1]. While most of these evergreening strategies conform to the letter of the law, very often they seem to undermine the spirit in which patent laws were created.

For major pharmaceutical companies, revenues come primarily from one or two of their blockbuster drugs (defined as drugs producing revenues in excess of $1 billion a year), such as Lipitor and Celebrex from Pfizer and Allegra from Aventis. Having spent years of colossal investment, both in time and resources, the branded pharmaceutical companies mobilize all their resources to reap the bountiful benefits as their products move from “on the shelf” to “off the shelf.” However, innovator organization can harness this opportunity only for 20 years, since after that the formula enters the generic arena and the price can decline by one-fifth of the initial. For instance, the sales of Capoten, manufactured by Bristol-Myers Squibb, plummeted from $146 million to $25 million within 12 months after the expiration of its patent in the US [2]. The expiration of a patent brings in its wake generic versions of the drug which make considerable inroads into the markets of brand-name drugs.

Therefore, it is important for the pharmaceutical companies that the life cycle of their drugs be prolonged to as much as possible. Developed economies with technological prowess take this initiative for cutting-edge R&D and aim to create

* Corresponding author. Tel.: +91 (361) 2582214; fax: +91 (361) 2582249.
E-mail addresses: lrangan@yahoo.com, lrangan@iitg.ernet.in (L. Rangan).
[1] This authors are contributed equally in this work.

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a technology transfer of the generic formulas beyond geo/economical/political boundaries. Thus evergreening has emerged as an important strategy among the major pharmaceutical companies in the US and Canada for life- cycle management of their products, in order to retain profits from their drugs.

2. Patentability of a drug

An understanding of what makes a drug fit to get a patent and what features in a drug can be patented is essential for an understanding of the mechanics of evergreening. To qualify for a patent a drug must, just like any other invention, satisfy the three basic criteria of novelty, of being non-obvious (manifested in the inventive step of the invention), and of being industrially applicable. The inventor can patent the product (the drug in this case), the process of manufacture, as well as methods of use of the product. Although the criteria might appear straight forward, the manner in which it is interpreted and applied is of critical importance in deciding what is fit and what is not to be granted a patent. Probably nowhere is this brought out more clearly than in the case of pharmaceuticals.

Traditionally, pharmaceutical companies filed patents for only the primary properties of a drug, such as the active ingredient, primary use, formulation, processes and intermediates involved in manufacturing the drug. However, in the quest of sustained profits and market exclusivity, companies now file greater numbers of patents for a single product. Very often these patents cover an expansive number of uses, packaging of the drug, dosing regimen, dosing route, dosing range, methods of treatment, delivery systems, combinations, biological target, metabolites, polymorphic compounds, stereoisomers etc.

Clearly, the patent laws cover everything ranging from colour of the tablet to the process for making it. In fact, even metabolites produced inside the body of the patient after ingesting the drug have been patented (US Patent No. 4636499 and Patent No. 6150 365). With such latitude, the inventor can keep adding patents to the same product and extending his or her monopoly over the product.

3. Branded versus generic drugs

Patent law does not distinguish between inventions consisting of "brand new products" and inventions relating to improvements; the same criteria for patentability apply. Taking the advantage of this existing loophole in patent law, not only those who develop an original product file patent applications relating to developments or modifications of their products, many applications are also in fact filed by other companies, including generic companies. Thus, the patent regulatory organizations have become an amphitheatre for the branded and generic medicine makers. While branded companies advertise to customers and health organizations about their brand value and reliability, and try to cast generics negatively on the basis of poor replication, or unsatisfactory testing before commercial production of the original formula, the capitalistic approach weakens their competitor product thereby channeling "designing around" the patent.

By allowing patents for secondary developments, the branded companies not only fulfill the real goal of the patent system (patents as a reflection of technological progress) but also encourage other companies to get engaged in innovation. This is where the battle for the regulatory and business rights is being fought between the branded and generic medicine makers for an undistributed market profits. In the case of pharmaceuticals, there is a vested interest—the generic pharmaceutical industry—positioned to challenge bad patents. Brand makers have to undergo stringent field trials for new releases, while generic makers can avoid it by showing promising replicas in terms of chemical standards and benchmarks set by the brand makers. This disables malicious imitations of branded drugs and trusts new drug manufacturers entering the market to diffuse the deterrence from expensive field trials. What is clear though is that government regulations in the different countries will determine the extent to which pharmacies, doctors, hospitals and even patients can exercise that choice- in some countries the generic version is mandated under certain circumstances.

4. Evergreening strategies

It is not surprising to note that the giant pharmaceutical companies no longer wait for the expiry of their patent(s) to begin the evergreening process. In order to extend their monopoly and control, strategies to extend patents and avoid generic competition are formulated as soon as the product is ready for patenting. These 'strategies' or "life cycle management plans" include not only patent related strategies, but other practices of delaying or limiting generic competition in the market as well. This section discusses some common evergreening strategies, generally in context of the pharmaceutical industry.

4.1. The 30 month stay provision

When a company makes a new drug, it must get regulatory approval from the Food and Drug Administration (FDA) showing that the product is safe and effective by filing a New Drug Application (NDA). This ensures that the drug can be sold in the US. To protect against intellectual property infringement, the makers go for patenting their product. A drug approved by the FDA is listed in an FDA publication called Approved Drug Products with Therapeutic Equivalence Evaluations, more commonly referred to as the "Orange Book". Any new patents associated with the drug must also be listed by the drug maker in the Orange Book [3].

Under the 1984 Hatch-Waxman amendments to the Food, Drug and Cosmetics Act, a generic drug manufacturer wishing to make generics of a brand-name drug must file an Abbreviated New Drug Application (ANDA) with the FDA. The ANDA needs to satisfy the FDA that the generic is a bioequivalent of the brand-name drug. Furthermore, the generic must not be in violation of any patents on the brand-

i) the drug has not been patented;
ii) the patent has already expired;
iii) the generic will not enter the market till the patent expires;
iv) the patent is invalid or will not be infringed by the generic.

If the generic manufacturer certifies to the fourth option (called a "paragraph IV certification") then it must immediately send a notice to the patent holder informing its intent to market a generic. A paragraph IV certification triggers the right of the brand-name company to challenge the generic manufacturer in court within 45 days on the basis that the generic is in violation of a patent listed in the Orange Book. This is where the catch lies: if the brand decides to litigate, the statute automatically prevents FDA approval of the generic for 30 months or until the litigation is resolved or the patent lapses, whichever occurs first.

Companies have misused this provision and at times have gone to the extent of listing bogus patents in the Orange Book to gain time by litigation. The problem here is that merely challenging the generic in court gives the brand an automatic extension of two and a half years. The brand could litigate saying that the generic violates one of the patents listed in the Orange Book and get a 30 month extension, irrespective of whether the challenge was correct or whether the patent was valid. In theory, with n number of patents listed in the Orange Book, the brand could go on litigating for 30n months or till the patent lapses by initiating a separate litigation for each listed patent. According to a US Federal Trade Commission (FTC) analysis, approximately 72% of brand-name companies took advantage of this provision [4].

4.1.1. A case study: Bristol-Myers Squibb and Taxolc

Bristol-Myers Squibb (BMS) sells paclitaxel, used to treat ovarian, breast and lung cancer, under the brand-name Taxol. Paclitaxel was developed by the National Cancer Institute and placed in the public domain and hence was not patentable. The drug was approved by the FDA in December, 1992. According to FDA regulations, BMS was given a five-year market exclusivity over sales of paclitaxel as Taxol until December, 1997.

However, before expiration of the five-year period, BMS obtained two patents on paclitaxel for methods of administering it as an anti-tumor agent and sought to extend the five-year exclusivity [5]. Upon expiration of the five-year term in December 1997, a number of generics tried to enter the market. BMS challenged many of them based on its patents listed in the Orange Book and got an extended monopoly for 30 months after 1997. This prevented the entry of generics into the market until 2000 when the sales of Taxol peaked at $1.6 billion. Eventually the courts ruled that the BMS patents were invalid, except for specific parts which by themselves could not have blocked the entry of generics into the market.

In June 2002 attorneys general of 29 US states filed a lawsuit against BMS alleging that in 2000 it started the process all over again by acting in collusion with a California-based company, America BioScience. According to market, once again with the aid of the 30 month extension. The issue is still in court.

4.2. Patent strategies I – line extension

An area of rapid and well-publicized growth in 2005 was the generic market, which grew by 13% in the top eight countries to $55 billion. Along the way, generic prescription volume surpassed branded volume for the first time in US history. As generic drug manufacturers became more aggressive in their efforts to gain share in markets formerly dominated by branded products, companies with significant brand franchises tried to protect their revenues by going after line extensions, defending patents, and reallocating their product portfolios.

Apart from the primary patents on a drug, a manufacturer can apply for more patents on the drug in order to extend its monopoly on the drug. This process is called "stockpiling." Here, the brand-name companies "stockpiles" patent protection by obtaining separate 20-year patents on multiple attributes of a single product. The expiration of these patents can extend market exclusivity by several years in addition to the period of the primary patent. Line extension refers to such strategies where companies attempt to buy additional period of exclusivity by gaining patents on modifications to the drugs or their method of use.

One of the fundamental premises of the patent system is that patents be granted to inventions that are original. Indeed, objections would be invalid to extension of patents over inventions that are genuinely original. However, in the context of the pharmaceutical industry the emerging practice is to protect a cluster of related technologies by filing secondary applications even when these related technologies are not entirely original or fit to be called inventions. What this effectively does is reset the clock on the protection period sustaining the market exclusivity for the drug.

As mentioned earlier, it is not unusual to patent such aspects of a drug as packaging, dosing, methods of treatment, delivery systems, combinations, biological targets etc. Upon ingestion of a drug the body might convert it to into a metabolite which has the actual therapeutic effect. Some companies have even filed patents for these metabolites with a view to stymie the introduction of generics into the market - since the metabolite is patented, any patient consuming the generic and hence producing the metabolite in her body would be in violation of the patent. Some possible types of secondary patents are:

- Composition patents
- Patents for new polymorphs
- Patents for new formulations
- Synthesis patents
- Patents for new therapeutic regimes
- Patents for metabolites or pro drugs, etc.

4.2.1. A case study: Pfizer and Viagra

In 1991 and 1992 Pfizer obtained patents on a series of

sildenafil citrate, marketed by Pfizer under the brand-name Viagra. The patents stated that these compounds were useful in the treatment of angina and hypertension. Subsequently, several research articles were published in 1992 and 1993 suggesting that PDE inhibitors could be useful in the treatment of impotence and male erectile dysfunction (MED) [6,7]. Pfizer followed this by filing for new patents in 1994 which covered the same compounds patented in 1991 and 1992 but claiming that these products could be used to treat impotence and MED (US Patent No. 6469012). The claim stated that this use had been found "unexpectedly" and had the added advantage of being administered orally as opposed to existing medication which needed to be injected.

Lily ICOS, a joint venture of ICOS Corporation and Eli Lilly, challenged this patent arguing that in view of the articles published in 1992–1993 the invention was invalid for obviousness. Pfizer defended by saying that the patent was inventive in the respect that the articles did not suggest the compounds as an oral treatment.

The matter reached the courts in November, 2000. The judge found that the only difference between prior art and the claims was the suggestion of oral use, which did not constitute inventiveness. He declared the patent invalid. When Pfizer appealed against the decision, the Court of Appeal upheld the decision. The court observed that while there was reason to doubt that PDEs could administer orally to treat impotence and MED, simply deciding to try it out was not inventive. Moreover, there was nothing in the specification which suggested that there were any difficulties in oral administration which needed to be overcome by adapting the compound for oral use. It was obvious to try and any skilled person carrying out routine procedures would have been successful.

4.3. Patent strategies II – franchise extension to successor drugs

The struggle between the brand and generics now has taken a leap beyond. Brand makers are extending their patents beyond the expiration dates by creating euphoria about the most original and enhanced drug effects based on brand reliance and constant improvisation in the chemical composition which they ought to get it re-patented, thus an effort to curtail the generics entering the market. This strategy of "patent to patent" is being used to retain market shares by presenting consumers with a new, supposedly improved, drug line to replace the original drug whose patent is about to expire. This kind of switching of patients to the new drug line minimizes market share loss by attrition of consumers and at the same time dissuades generic drug manufacturers from entering the market with a generic for the original drug since most patients have already transitioned to the new drug. Obviously, such a large scale franchise extension requires promotion on a gargantuan scale. Companies invest huge amounts of money to launch massive campaigns to popularize the successor drug among patients. Doctors' offices are flooded with sales representatives offering them gifts of money and kind for prescribing advertisement campaigns do succeed in convincing both patients and doctors otherwise.

A number of countries now provide for extended patent terms for pharmaceuticals. These include Australia, Japan, Korea, Israel, the United States, and the member states of the European Union. Although there are no internationally agreed standards for patent term extension, the provisions for patent term extension in those countries that provide for it contain some common features:

- Extension is not automatic; the patent owner must make a specific application;
- The length of the extension granted depends on the length of time between the date of filing of the patent application and the date of marketing approval;
- A maximum extension of 5 years is provided for;
- The rights of the patent owner in respect of the patent are usually limited during the extended term compared with the rights available during the original term.

Although some countries do provide for patent term extension for pharmaceuticals, many countries do not. These include Argentina, Brazil, Canada, China, Colombia, Ecuador, Hungary, India, Malaysia, Peru, South Africa and Venezuela.

4.3.1. A case study: AstraZeneca and Prilosec

Omeprazole is proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer and gastroesophageal reflux disease. It was patented by AstraZeneca which marketed it under the brand-name Prilosec (US Patent No. 6090827). It is one of the best selling prescription drugs in history and towards the last five-years of its patent, which expired in April 2001, its sales amounted to about $26 billion.

Prilosec is a racemate containing equal quantities of both the S and R enantiomers. In most patients, except those that are "poor metabolizers", the racemate undergoes a chiral shift *in vivo* to form the S enantiomer, which is the active form of the drug. Before the patent on Prilosec could lapse AstraZeneca developed a new drug branded Nexium which was nothing but the S enantiomer, or the active component of Omeprazole. The company executives surmised that this formulation could be more effective against erosive esophagitis as compared to Prilosec. The company sanctioned four different studies to compare the efficacy of Nexium with Prilosec in patients with this condition.

The four studies compared 20 mg of Prilosec against a double dose of 40 mg of Nexium. The company justified this by saying that it planned to seek approval for a 40 mg dose of Nexium against erosive esophagitis for which a 20 mg dose of Prilosec is recommended. Of the four studies two concluded that Nexium did not surpass Prilosec even with this increased dose. However, two studies found Nexium better than Prilosec. The results of the favorable studies were published while those of the other two studies were not released.

There was one study comparing equal dosages of 20 mg for both Prilosec and Nexium. No difference in healing rates was found during the initial course of treatment. At the end

was used to convince doctors that Nexium was indeed better than Prilosec. Acting quickly, AstraZeneca got FDA approval for Nexium in February, 2001 – a few months before the patent on Prilosec was to expire. At the same time AstraZeneca exploited the federal provision of pediatric exclusivity in the US which gives a six month extension on existing market exclusivity for conducting tests on effectiveness of a drug on children. This extended the exclusivity of Prilosec fending off the generics for a further six months.

The extra time gained was used to campaign for the drug. AstraZeneca launched one of the most massive marketing campaigns in the history of the USA after it got the FDA approval. The company spent $500 million a year on direct-to-consumer marketing, hospital discounts on the drug, free samples for doctors and media advertising. All this effort resulted in a substantial fraction of the patients transferring to Nexium. In 2001 alone the company transferred 40% of Prilosec users to Nexium and managed a 9% growth in its gastrointestinal franchise (Fig. 1).

5. Effects of evergreening

When a drug goes off-patent and generic competitors enter the market, the price of the drug inevitably plummets. The lower price of the generic motivates most consumers to shift from the brand-name forerunner drug. When Glucophage, an oral antibiotic agent, went generic in late January 2002, more than 80% of prescriptions were captured by generics within two months. The percentage rose to 90% within six months.

As stated earlier, most of the pharmaceutical giants earn their major revenues from a couple of blockbuster drugs. A blockbuster drug losing its market exclusivity means huge drops in revenues for the company. Obviously, companies want their monopoly on such drugs to sustain and evergreening has emerged as major strategy towards this end. This section examines the implications of evergreening for the stakeholders in the market of drugs.

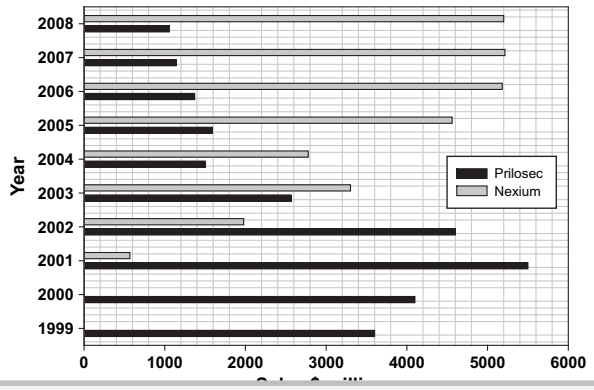
5.1. The branded drug company

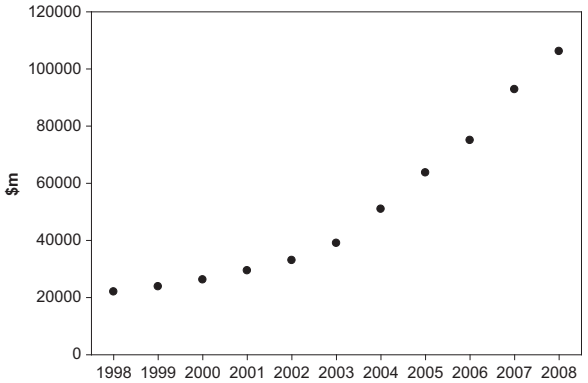
Pharmaceutical companies invest billions of dollars in drug research. It is estimated that of every thousand potential drugs screened, only four or five reach clinical trials and of those, only one is actually approved for marketing. With the odds stacked so heavily against them, it is reasonable for pharmaceutical companies to obtain market exclusivity rights and recover the costs of research and further profits through appropriate pricing mechanisms. Problems arise when these companies attempt to exploit loopholes in the regulatory system to unduly extend their monopoly over the market in a bid to sustain their revenues. With an ever growing generic drugs industry (Fig. 2), such attempts by the branded drug industry have become even more aggressive.

At the same time, evergreening carries a high risk even for the company seeking to exploit it. Consider franchise extension through successor drugs. Even if the successor drug is not an entirely new invention, its final approval does entail all the steps from synthesizing the new drug to clinical testing. This means that the company still incurs substantial costs in R&D of the successor drug. In such a scenario, if the new drug lacks the expected level of efficacy, is proven unsafe, fails to gain regulatory approval for some other reason or fails to sustain market shares of the original drug, then the company risks losing a lot of money.

In 2002 Schering-Plough introduced Clarinex as a next-generation drug for Claritin. Things went wrong when the approval of Clarinex by FDA got delayed and generics got a chance to enter the market. A sufficient number of Claritin patients could not shift to Clarinex, and Schering-Plough faced a double disappointment: Clarinex could not scale the blockbuster status of Claritin, and because of generics the sales of Claritin plummeted from $3 billion to $300 million in a short time (Fig. 3), even though Claritin was converted to an over-the-counter (OTC) drug.

Most evergreening strategies invariably involve lengthy litigation. Even though pharmaceutical majors are in a better position to litigate than most generic drug manufacturers, it is definitely a financial burden. The practice has grown to such proportions that branded drug companies have started complaining about the costs of litigation involved in disputes over multiple patents. In any case, when evergreening strategies are well planned in advance they seem to work well for branded drug manufacturing companies.





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