



# STRATEGIES FOR DRUG PATENT EVER-GREENING IN THE PHARMACEUTICAL INDUSTRY

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*Abstract: Drug patent ever greening is a marketing strategy that multinational pharmaceutical companies have been using. In the past, the ever greening process has caused some major controversies in the Indian pharmaceutical industry. It has been used by manufacturers of a particular drug to restrict or prevent competition from manufacturers of generic equivalent. Thus, extending the patent period and seizing the generic drug manufacturing which overall incurs additional cost burden that can be very significant for the public health budgets and the consumer. The research article will focus on the various ever greening strategies utilized by drug makers. And will highlight the importance of Section 3(d) which helps discourage the abysmal practice of the pharmaceutical companies from ever greening of patents.*

*Keywords: Ever greening, patents, Pharmaceuticals, Section 3d*

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## 1. Introduction

Under the Indian patent law, a patent is a set of exclusive rights granted by a sovereign state to an inventor or assignee for a limited period of time in exchange for detailed public disclosure of an invention. An invention is a solution to a specific technological problem and is a product or a process. Once India became a signatory to the TRIPS agreement, India has periodically amended its Patent Law in order to be TRIPS-compliant. The latest amendment to the Patent Act was brought into effect from January 1, 2005. Article 33 of the TRIPS Agreement provided for a term of protection for patents for at least 20 years from the date of filing of the application.



Consequently, patent laws of all countries which are signatories to the TRIPS agreement provides for a patent term which is 20 years from the filing date of the application [1].

Drug patent ever greening is a marketing strategy that multinational pharmaceutical companies have been using. Ever greening is a method by which technology producers keep their products updated, with the intent to maintain patent protection for longer periods of time than would normally be permissible under the law. It refers to increasing the life of the patent or the patent term beyond 20 years to reap the benefits for a much longer period of time. Ever greening refers to a variety of legal and business strategies by which technology producers with patents over products that are about to expire retain royalties from them, by either taking out new patents (for example over new delivery systems, strength, indication or new pharmaceutical mixtures/formulations), or by paying for delay or buying out competitors, for longer periods of time than would normally be permissible under the law [2].

The ever greening process has caused some controversies in the pharmaceutical industries. It may be used by manufacturers of a particular drug to restrict or prevent competition from manufacturers of generic equivalent. Thus, extending the patent period seizes the generic drug manufacturing and additional cost burden which can be very significant for the public health budgets and ultimately the consumer.

Once the generic drugs are launched, the price of the patented drug can drop by as much as 90%. And, ever greening process helps in extending the exclusivity of the manufacturer over the drug, however this process leaves a wide gap between innovation and access. Competition leads to innovation and prolonging the patents for technologies may freeze the development and utility of the product.

## **2. Research methodology**

The research paper is based on Secondary research methodology and a case study approach.



### 3. Results

#### 3.1 Strategies for ever greening of patents:

Ever greening strategies usually followed by the pharmaceutical industries include:

**3.1.1. Redundant extensions and creations of 'next generation drugs' which result in superfluous variation to a product and then patenting it as a new application.** Various aspects of drug development are eligible for patenting include methods of manufacture, methods of medical treatment, chemical intermediates, formulations, mechanisms of action, packaging, delivery profiles, screening methods, and biological targets. Often these additional patents are sought shortly before the primary patents expiration. Therefore, if a brand-name drug company discovers a new chemical compound for treatment of a particular disease, it may file patent applications covering various aspects of the drug, all of which may have a different expiry date. Under such circumstances, a generic drug company may begin selling products that employ the same active ingredient, when the all the listed patents expire. Or else, it must instead use non-infringing process in order to market its product. Therefore, despite the need for differentiation to satisfy the conditions set forth by the IP laws, if the patients are to be convinced for a successor product, a certain degree of commonality with the popular and trusted original brand is important.

For example, when Prilosec (marketed as Losec in the UK) was swapped for Nexium in the market, the drive to equate the new brand with the older blockbuster included the design of the pills appearance. AstraZeneca made Nexium purple and very similar looking to the original Prilosec.'

**3.1.2 Prescription to over-the-counter (OTC) switch.** The process of reclassifying drugs from prescription to OTC status is referred to as an "Rx to OTC switch." [3] Drugs are commonly switched one of two ways: under the "OTC drug review," or by a manufacturer's submission of additional information to the original new drug application. All the drugs those can be used safely administered without professional supervision can be sold as OTC drug. By following the labeling, consumers can use it safely and effectively without professional



guidance. Labeling is therefore, an influential element in the OTC risk-benefit comparison and can alert consumers to such potential problems.

Principally, an ingredient is introduced as an OTC medicine; it is typically marketed by a manufacturer as a prescription medicine first. Sequentially, after a sufficient amount of time has passed to enable the manufacturer to gather appropriate scientific information on the product, the manufacturer may elect to submit a new drug application, or NDA, to FDA so that it may be considered for OTC status. The FDA review involves weighing a drug's safety against its benefit to patients. FDA also considers whether consumers will be able to understand and follow labeling directions, whether patients can self diagnose the condition or at least recognize the symptoms they want to treat--and whether routine medical examinations or laboratory tests are required for continued safe use of a drug.

According to IP experts, the strategy to launch a patented prescription drug in an over the-counter (OTC) form prior to expiration of marketing exclusivity is a way to build up an OTC market position against future competition. Launching a OTC version of an approved drug prior to patent expiration and promoting consumers to switch to newer formulations of drug products from earlier formulations ... for which patent protection has not yet, but is soon to, expire, and thus undercuts the market demand for generic versions of the older formulation; each of these approaches is said to allow “innovator firms to maximize their monopoly period.

Another advantage that the companies get from Rx-to-OTC switch is stipulated by the IP laws. Under the law, OTC drugs may be advertised directly to consumers without the many restrictions placed on prescription products. OTC status provides a better opportunity for direct communication with the patient (consumer), advertising in magazines and television, packaging, brochures, and retail displays.

***3.1.3 Exclusive partnerships with cream of generic drug players in the market prior to drug patent expiry thus significantly enhancing the brand value and interim earning royalties on the product.***

This anticompetitive practice is followed widely by innovator companies which try to



prevent the entry of corresponding generic product in the market. The innovator company enters into a settlement agreement with the generic manufacturers to delay or eliminate specific generic drugs from entering the market place. “Pay for delay” agreements are a form of patent dispute settlement agreement in which a generic manufacturer acknowledges the patent of the originator pharmaceutical company and agrees to refrain from marketing its generic product for a specific period of time. The generic manufacturer, in return, receives consideration in the form of huge payments from the originator.

These “pay-for-delay” patent settlements effectively block all other generic drug competition for a growing number of branded drugs. According to an FTC (Federal Trade Commission) study, these anticompetitive deals cost enormously to consumers and taxpayers approximately, \$3.5 billion in higher drug costs every year. Since 2001, the FTC has filed a number of lawsuits to stop these deals, and supports legislation to end such “pay-for-delay” settlements [4].

**3.1.4 Defensive pricing strategies or competitive practices wherein the innovator companies ensure healthy competition with generic players.** Generic companies begin selling generic medicines in the market at a price that was, on average, 25% lower than the price of the originator medicines prior to the loss of exclusivity. Two years after entry, generic medicine prices are on average 40% below the former originator price. The market share (in volume terms) that the generic companies attained is about 30% at the end of the first year and 45% after two year [5]. However, there are competitive strategies by which the brand name manufacturers to respond to generic competition. For eg. Innovator companies can decrease the price of the product in line with the generic players or introduce improved drugs that leave the generic entrant a generation behind.

Similarly, “authorized generics” are generic versions of a branded drug, issued by the branded drug manufacturer. Brand name companies do not routinely place authorized generics on the market, but their production can be a tactic to deter entry by generics



manufacturers. However, evidence indicates that consumers may benefit from authorized generics, even when third party generics are already in the market.

Biosimilar drugs are subsequent versions of earlier biologic drugs. Such drugs are more complex and expensive to develop than small-molecule pharmaceutical products. In the US, a special legislation passed in May 2010, Biologics Price Competition and Innovation Act, provides the reference listed biologic drug with a data exclusivity period of 12 years, during which no biosimilar product can be approved for sale. Follow-on biosimilar drug entry by generic companies is therefore delayed.

**3.1.5 Establishment of subsidiary units by respective innovator companies in generic domain before the advent of rival generic players.** Several Big-Pharma companies are showing an increased interest in diversification strategies such as building a position in generics or establishing subsidiary units in generic domain before the advent of rival generic players. Over the past decade, most of the Big Pharmas have adopted small molecule generics to expand their overall business model. Principally, they observe three distinct strategies to participate in the generics industry, with some adopting more than one of these:

1. Authorized Generics
2. Emerging Market Branded Generics
3. Fully-fledged Generics Divisions

Of the twelve pharmaceutical companies with the highest global revenues from prescription pharmaceuticals in 2013, only Abbvie and Hoffmann-La Roche are not proactively adopting at least one of the above strategies. Teva, on the other hand is more well-known as a generics company (despite having a strong portfolio of patented products).

Novartis, through Sandoz, its generic-drug business, had sales of \$7.5 billion in generic drugs in 2009 and added to that position further by acquiring the generic oncology injectables business of EBEWE for EUR 925 million (\$1.3 billion).

In March 2010, AstraZeneca (London) signed a license and supply agreement with the Indian drug manufacturing company Torrent Pharmaceuticals, under which Torrent will



ensure the supply a portfolio of generic medicines to AstraZeneca for emerging markets. In 2009, Glaxo SmithKline (GSK, London) partnered with India's Dr. Reddy Laboratories under which Dr. Reddy's will manufacture and supply drugs to GSK, and will thus, license and co-market the drugs in various countries in Africa, the Middle East, Asia-Pacific, and Latin America. In December 2009, GSK entered into a strategic partnership and acquired a 19% stake in the South African pharmaceutical company Aspen PharmaCare to serve emerging markets [6].

**3.1.6 Brand migration.** Innovator companies use brand migration as an alternative to extend their product life cycles and delay competition where in when one "brand name" product patent and its associated exclusivity is near expiry, innovator companies start directing patients' attention to the company's other products viz a new branded product that is heavily promoted to both patients and physicians. For example, Astra Zeneca before expiration of the product patent on Prilosec (omeprazole) started an attempt to move patients' attention towards its patented successor Nexium (esomeprazole magnesium). Thus in this way by "brand migration" these companies extend product life cycles.

*AstraZeneca's Nexium – a case study.* Prilosec (also known as Losec) is a proton-pump inhibitor (PPI) used to treat heartburn and was AstraZeneca's (AZ) most profitable drug. By 2000, Prilosec was the most prescribed drug in the world, with global sales reaching \$6 billion. However, Prilosec's patent was set to expire in 2001, so it was loss of brand name protection and assured competition from generic drug manufacturers which posed a financial vulnerability to AZ.

AZ pulled a massive 'bait and switch' on the American public. Rather than venturing in new drugs that would be an incremental innovation for patients, they poured millions of dollars into promoting a drug that was far more expensive but no better than equally effective generic drugs. They claimed that Nexium (successor) was proven more effective at acid inhibition than comparable drugs. However, the clinical trials alluded to in these ads only compared Nexium at dosage levels twice those of Prilosec (40 mg to 20 mg respectively). No tests were done to compare 40 mg of Nexium to 40 mg of Prilosec.

Nexium was approved in February 2001, months before Prilosec's first patent loss later that year, The company did employed an aggressive marketing strategy to detail doctors and hospitals, and handed out masses of free samples. Such a strategy paid off, Nexium sales gathered a huge momentum while Prilosec's



continue to wane. As of 2002, 40% of Prilosec patients had switched to Nexium, which notched up sales of \$3.9 billion in 2004. Thus, AZ had actually managed to grow its overall GI franchise - by nearly 9% from 2001 to 2002. Interestingly, by 2009, doctors prescribed- and patients worldwide consumed-\$7.8 billion worth of evergreened Nexium rather than Prilosec according to IMS health.

Transitioning patients from a blockbuster drug like Prilosec to a generic counterpart or other class of drug can cause episodes of pain or discomfort. AstraZeneca's massive efforts thus successfully warded off generic competition and kept it among the upper echelon of the GI market.

**3.1.7 Two is better than one.** Launching combination products is another ever greening strategy which is rising in popularity. Drug manufacturers are combining the threatened product with another branded drug product to treat two concomitant conditions with one therapy. The combination can thus, reclaim its unique position beyond the reach of the generic [7]. Companies can also evergreen their patents by combining formulations or producing slow-release forms of an existing drug. Such 'follow-on' products then compete with generics introduced after the patent expiry of the originator drug. In all cases, follow-on products are heavily promoted by the drug manufacturer to ensure that they are prescribed over the older versions, even if they lack experimental evidence of comparative efficacy or safety. Other strategies include, single-isomer versions marketed in place of enantiomeric drugs (e.g., levocetirizine and cetirizine), combination products marketed in place of unitary products (e.g., simvastatin/ezetimibe and simvastatin), and slow-release formulations (e.g., extended-release zolpidem and zolpidem).



**Case study: Efexor to Efexor-XR to Pristiq.** Drug venlafaxine (marketed as Efexor) had major side-effects. However, when administered in extended release form these side-effects were substantially reduced. Therefore, the extended release form (Efexor-XR) became the drug of choice. Although it might seem obvious to combine venlafaxine with an extended release form to overcome the side-effects, the patent office granted two new patents for the extended release versions of venlafaxine. This resulted in delayed generic entry by two and a half years, while the legal proceedings took place. Finally, the evergreening patent was declared invalid. However, the cost to taxpayers of this delay was estimated to be \$209 million.

Wyeth has a second ever greening strategy for venlafaxine. Venlafaxine is metabolized by the human body to desvenlafaxine. In other words, desvenlafaxine is a variant of the original active pharmaceutical ingredient venlafaxine. Clearly the two compounds were closely related. Therefore, it is astonishing that desvenlafaxine passed the tests for getting a patent.

Desvenlafaxine is marketed as Pristiq. From a business perspective, Pristiq is essentially a patent extension for Wyeth. Effexor XR, which had blockbuster sales of \$3.8 billion in 2007, was gradually losing patent protection, and Wyeth was hoping to convince psychiatrists to switch patients from Effexor to Pristiq. Pristiq entered the market early in the two-and-a-half-year period of legal wrangling over the extended release venlafaxine (Efexor-XR) patent. Wyeth's marketing of Pristiq in February 2009 was so lavish that it attracted the attention of investigative journalists. Despite having no additional benefits for patients, during the first six months of 2014 half of prescriptions were written for Pristiq rather than for the clinically identical Efexor-XR.

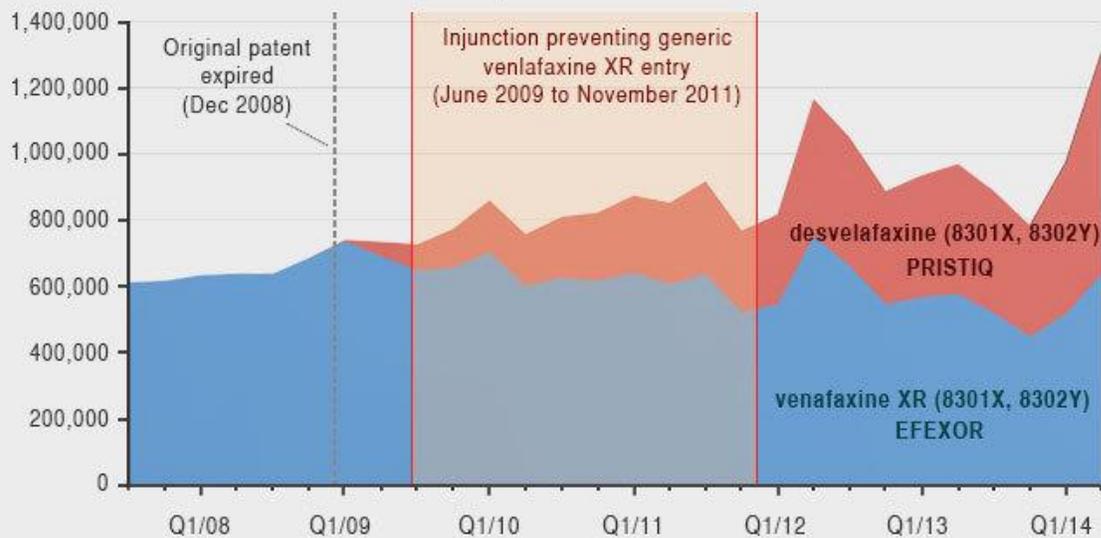
Interestingly, Pristiq costs between \$A22.32 and \$A26.50 more than Efexor-XR, depending on the dose administered. Based on reported prescription volumes in 2013-14, the cost to the taxpayers who were prescribed Pristiq rather than Efexor-XR exceeded \$21 million a year. Unless generic companies challenge the additional desvenlafaxine patent, no generic versions of Pristiq can be launched until August 2023, when the patent expires.



## Prescribing shift: Efexor to Efexor-XR to Pristiq

The evergreening strategies used for the drug venlafaxine, owned by Pfizer

### Volume of prescriptions



Venlafaxine (Efexor) is a depression drug first patented in 1983.

Pfizer's extended release (XR) patent for venlafaxine (Efexor XR) was not due to expire until 2023, but was found to be invalid and revoked in late 2011.

In 2001 two new patents were sought for desvenlafaxine (Pristiq) which is simply a *variant* of venlafaxine. These patents do not expire until 2023.

Though Pristiq has no additional benefits for patients and costs over \$22 more than Efexor-XR, about **half of prescriptions** are now for Pristiq.



#### 4. Discussion

In 2005, India amended the Indian Patent Act to curb ever greening practices adopted by the Pharmaceutical manufacturers. As a major move, Section 3(d) was incorporated in the Indian Patent Act which stated that:

“The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process results in a new product or employs at least one reactant. Explanation - For the purpose of this clause, salts, esters, polymorphs, metabolites, pure form, particle size, isomers, and mixture of isomers, complexes, combinations and other derivatives of known substances shall be considered to be same substance, unless they differ significantly in properties with regard to efficacy. [8]”

In essence, section 3(d) aims to check ever-greening by providing that only those pharmaceutical derivatives that demonstrate significantly enhanced “efficacy” are patentable. Section 3(d) draws a line between ever-greening and incremental innovation. The mere reading of the said section clearly recites as to what is not patentable. In other words if the “prospective patent” substance results in the enhancement of the known efficacy of the substance then it is patentable. The section only tries to filter out any frivolous inventions made in an attempt to ever-green patent incorporating trivial changes unless such changes result in significant improvement in the efficacy. It is worthwhile to mention that Section 3(d) was enacted by the legislature only with the intent of discouraging the abysmal practice of the pharmaceutical companies from ever greening of patents.

It was observed that under Section 54 of the Patent Act, patent of addition may also be granted for an improvement in or modification of an invention in respect of the main invention. (Though the life of such a patent granted for improvement is set to expire with that of the main invention). This should support the debate as far as any questions relating to the grant of patents for incremental inventions are concerned.

Such legislations thus, act as safeguards against evergreening, and prevent the practice of evergreening of patents. The prolonged debate over its potential effect on the grant of pharma



patents has also been going on for some time. In fact it was the Novartis case that challenged the constitutionality of the section 3D and its compatibility with TRIPS after the rejection of its patent applications over its anticancer drug Glivec by the Patent Office in 2013. In another case, India's Intellectual Property Appeal Board (IPAB) revoked a patent granted to GlaxoSmithKline (GSK) for its breast cancer drug Tykerb in a reinforcement of the country's hard line on "incremental" inventions in the pharmaceutical field [9, 10].

## 5. Conclusion

India has been facing criticism in the past, particularly by Big Pharma companies, for not adequately fulfilling its obligations under TRIPS to provide patents for novel pharmaceutical incremental innovations. However, generic pharmaceutical manufacturing is the main stay for the industry in India and therefore, the government will be under increasing pressure to supply low-cost drugs to an ever increasing population. With Big Pharma increasingly taking advantage of secondary innovations, such as specific salts or enantiomers, specialized delivery systems, to improve their overall viability; further conflicts between pharmaceutical companies and the Indian patent system are expected in the near future.

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