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Ever-greening in Pharmaceuticals: Strategies, Consequences and Provisions for Prevention in USA, EU, India and Other Countries

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Abstract

Pharmaceutical research and development is an expensive, time consuming and uncertain process that may take 8-10 years to complete. Patent clock starts much before a new drug is approved for marketing and significant amount of time may be lost in the review and approval process by regulatory bodies. So in order to recoup the considerable time and resources invested in the drug development and approval process the pharmaceutical companies depend on exclusivity provisions granted by the regulatory bodies. There are several official and unofficial methods to extend term of a patent beyond 20 years, Official methods include provisions by some regulatory bodies such as Data exclusivity, Orphan drug exclusivity, Paediatric exclusivity and the 180-day exclusivity (Hatch Waxman Act, U.S. Food and Drug Administration), Supplementary protection certificate (European Medical Agency), whereas unofficial methods include altering or reformulate the existing compound to obtain a new patent by utilising polymorphism, creating combinations, stereo-selective/chiral switches, conversion to NDDS, OTC switching, authorised generics, etc. This article aims at highlighting the strategies used by Pharma giants to extend the term of their patent portfolio in order to maintain their monopoly for extended periods and the regulatory provisions in different countries to check these practices.

Keywords: Patents; Ever-greening; Generics; Drug exclusivity

Ever-greening

Ever-greening refers to the various ways wherein the patent holder attempts exploit the loopholes in patent laws and related regulatory processes in order to maximize their monopoly especially over bestseller drugs by filing disguised or artful patents on previously patented invention just before the end of the term of the parent patent. These additional patents are meant to protect the following aspects:

- Combinations of two or more drugs;
- Dosing rage and dosing route;
- Biological targets for old molecule;
- Delivery profiles, mechanism of action;
- Derivatives and isomeric forms;
- Screening methods, dosing regimen;
- Packaging;
- Different methods of treatment [1].

Ever-greening is a strategy acquired by the innovator companies to recover high costs incurred by them in Research and Development and as a means to legally protect any minor modifications that are intentionally made to the parent patent just to obtain multiple patents on the same drug and hence extend the overall term of the patent to enjoy monopoly for extended periods of time. In simple words, a company launches a drug product and obtains patent protection for it and just before the end of the term of that patent; the company files a new patent for a minor modification in the original molecule that extends the overall term of patent protection which ultimately contributes to their monopoly. Hence, extending the patent protection period delays or prevent the entry of the generic versions of the drug which can affect the budget for public health and finally the patient.

Example of ever-greening: Consider an innovator firm named SA Pharmaceuticals which formulates a new molecule for the cure of a specific disease. SA Pharmaceuticals applies for patent protection for the new molecule on 10 April, 2005. Once the application is approved by the patent office, it will result in a patent that will provide protection for the next twenty years (starting from the date of application) up to 10 April, 2025. If on 1 February 2010, SA Pharmaceuticals files a second application before the patent office, for a minor improvement in the previously patented molecule and that application is also approved, it will result in patent protection that will end on February 1, 2030. In this case a generic manufacturer may launch generic version of the parent molecule after 10 April 2025 but excluding the modifications that SA Pharmaceuticals had made to the original molecule, for which the patent protection term is set to end on 1 February, 2030.

Patent Term Extension Strategies Followed by the Innovator Firms Involve

The 30 month stay provision (USA)

For every new drug, it is compulsory to prove that the product is safe and effective in order to obtain regulatory approval from the Food and Drug Administration (FDA). Once approved, the drug gets entry into FDA's publication called Orange Book also called Approved Drug Products with Therapeutic Equivalence Evaluations (TEE), which serves as a reference for the generic manufacturers who wish to launch the generic versions of the drug after the end of the term of patent

protection. Additional patents that are linked to the parent patent are also too listed in the Orange Book [2].

The Hatch-Waxman amendment (1984) of the Food, Drug and Cosmetics Act requires a generic drug manufacturer planning to market generic version of a previously patented drug, to file an Abbreviated New Drug Application (ANDA). The generic applicant needs to satisfy that the generic is equivalent in activity when compared to the branded drug. The generic manufacturer also needs to certify that:

- Para I certification: The drug is not patented;
- Para II certification: The drug patent has already expired;
- Para III certification: The generic will enter the market only when the patent expires;
- Para IV certification: The patent is invalid or will not be infringed by the generic.

If generic applicant wishes to go for the Para IV certification, then it must intimate the decision to the patent holder. If paragraph IV certification is used the brand name company within 45 days from the receipt of the notice can exercise its right to challenge the generic applicant. If brand name company decides to challenge the generic application, the law automatically puts a stay on further generic approval for the next 30 months or until the hearing is resolved or the patent lapses. Although the provision aims at protecting the interests of innovator firms, still companies have misused this provision. US Federal Trade Commission (FTC) analysed that approx. 72% of innovators exploited the provision [3].

Redundant extensions and creation of 'next generation drugs'

The different attributes of drug development that can be patented include delivery profiles, methods of manufacture, chemical intermediates, formulations, packaging, biological targets, mechanism of action and method of medical treatment, etc. Often the innovator firms utilise one of these attributes to obtain additional patents shortly before the end of the term of primary patent. Hence, if a brand-name drug company formulates a new molecule for treating of a specific disease, the company is eligible to obtain patent protection for various attributes of the parent drug, these additional patents covering different aspects of the same drug will add to the overall term of the parent patent and will restrict a generic drug company to launch generic version.

Example: When the patent for Prilosec was near expiry, AstraZeneca in order to maintain the monopoly of the blockbuster drug Prilosec launched Nexium which was the same drug with minor changes in design and colour [4].

Switching to over-the-counter (OTC)

Drug products that do not require professional supervision and can be safely administered by the patient status the innovator just needs to shows the ratio of safety to benefit to the FDA and whether it will be easy for the patient to self-administer the drug product. OTC status encompasses many benefits major of them being the opportunity for direct advertising to consumers through different forms such as advertising in television, magazines, retail displays, brochures, and packaging without any restrictions which apply on prescription drugs which maximizes himself and are easily available without prescription are known as Over the Counter drugs. The process of reclassification of a prescription drug to Over the Counter is termed as Rx to OTC switch. Opting for OTC review is another strategy used by the innovators in order to maximize their monopoly over highly lucrative drug molecules. To get OTC the innovator's monopoly, therefore the OTC drug being from the innovator company would be preferred and this would effectively undercut the demand for generic version in the market [5].

Example: Nasacort 24 h (Sanofi) which was originally developed as intranasal steroid was switched for OTC in 2014 for the treatment of allergies [6].

Pay for delay or reverse payments

This is one of the anti-competitive practices that are followed by innovator firms to prevent or delay the entry of cheaper generic versions until their generic version of the drug has been firmly established in the market. The innovator firm signs an agreement with the renowned generic manufacturers to delay or give up the launch of generic version of drug. Pay for delay arrangements is a kind of settlement agreement between the innovator company and a generic manufacturer in which the latter agrees to refrain from marketing its generic version for a specified period of time in return for huge payments from the innovators. These pay-for-delay arrangements effectively block the entry of generics and thwart the generic competition until the innovator's drug establishes itself in the market. This type of arrangement is unlawful and Federal Trade Commission or similar agencies constantly look out for such deals [7].

Example: Servier was fined an amount of €330 million for delaying entry of generic high blood pressure medicine perindopril in the market, in 2013, Johnson & Johnson and Novartis were fined €16 million for delaying entry of generic version of pain-killer fentanyl [8].

Establishment of generic units by innovator companies

Pharma giants in order to compete with the generic players are showing an ever increasing interest in setting subsidiary generic units and entering partnerships with major generic manufacturers and building a position in generics before the competition from of rival generic players rise. Over the past decade, Big Pharma has acquired small generic units to expand their business model. Particularly the following three categories of partnerships are observed:

Examples: AstraZeneca and Indian generic manufacturer Torrent Pharmaceuticals signed up and agreement in 2010 under which Torrent will manufacture and supply generic versions for AstraZeneca's emerging markets.

Novartis established Sandoz as a subsidiary unit for manufacturing generic drugs and Novartis's profit in generics rose to $7.5 billion (until 2009), Novartis acquired generic business in oncology which further added to this profit [9].

Brand migration

Brand migration is another ever-greening technique wherein the innovator companies release a successor drug with a different brand name and with minor changes such as changes in design, colour dosage etc. to extend the overall term of highly lucrative blockbuster drugs in order to maintain the monopoly for longer durations. Innovator companies invest heavy amounts in the promotion of such new brand drugs.

Nexium case: AstraZeneca's Prilosec was a blockbuster and the most profitable Proton-Pump Inhibitor (PPI) of its time which was used to treat heartburn. By 2000, Prilosec sales reached $6 billion and it became the most prescribed drug in the world. Prilosec was to go off patent in the year 2001 which meant a huge loss to AstraZeneca's monopoly. Astra Zeneca rather than investing in incremental innovation for the existing drug invested huge amounts of money in the promotion of its successor drug 'Nexium' claiming that it was more effective than even Prilosec and other drugs in the same category. However, later clinical trials revealed that 40 mg of Nexium was being compared to 20 mg of Prilosec. No studies were conducted to compare 40 mg of Prilosec to 40 mg of Nexium [4].

Combination of two or more drug products

Another strategy that is gaining popularity among innovators is launching combination of two or more drugs and in fact United States and European Union have laws to provide supplementary patent protection on such combinations. Innovator firms are combining the soon to go off-patent product with another drug to provide treatment for two closely associated medical conditions.

This type of combinations may attain same position which the branded drug attained during the exclusivity period and such follow-on products provide a tough competition to the generics. Also huge amounts of money is being pumped the brand name company to ensure that their product is prescribed over the older versions, no matter if the combined product lacks experimental evidence of enhanced efficacy or safety [10].

Example: Venlafaxine earlier marketed as Efexor had some major side-effects. But these side effects were substantially reduced when the drug was administered in extended release form. In spite of the fact that combination of Venlafaxine with and extended release version of venlafaxine to overcome the side effects may seem to be obvious still two separate patents were granted by the patent office for the two versions of venlafaxine which in turn delayed entry of generics by two and a half years. However, at last the ever-greening patent was later declared invalid.

Defensive pricing strategies

Once the drug goes off-patent the generic companies start selling cheaper version of branded drug which is way too cheaper. Further the prices of generic version may drop below 40% or more within two years.

Innovators however have devised competitive strategies through which they respond to the increasing generic competition by decreasing the price of their generic version or by introducing improved generic versions at a much lower price that may leave a generic competitor a generation behind [11].

Innovator de-lists reference listed drug from orange book

In USA every innovator drug that is patented gets entry into the Orange book (Approved drug products with therapeutic equivalence evaluation), and before a generic gets approved it is necessary for the ANDA filer to prove that the generic version is comparable to innovator drug in bio-equivalence.

So the innovator drug serves as a reference for the launch of new generics and therefore de-listing is another tactic used by most of the innovator drug companies to significantly delay the entry of generics.

Example: Glenmark Generic Ltd vs. Ferring B.V

Ferring owned patent for DDAVP tablets, containing active ingredient as desmopressin acetate, Ferring applied to FDA for delisting the patent from orange book, in an effort to thwart Glenmark's marketing of launching its generic version. Subsequently Glenmark petition against the de-listing was accepted and the Glenmark's generic was approved [12].

Convert to Novel Drug Delivery System (NDDS)

Switching to Novel drug delivery systems by modifying a drug to use a different route of administration or developing its controlled, sustained or immediate release forms is another strategy used by innovators by which the NDDS may be patented. This effectively means the innovator continues to enjoy the price monopoly for the new patent term.

Example: Laboratories Fournier S.A. developed and obtained patent on immediate release composition of Fenofibrate in the year 2008, while the first patent for the original Fenofibrate was granted in 1973, after this several other compositions of fenofibrate were also granted patents, and thus thwarted generics competition.

Effects of ever-greening

As soon as a drug goes off-patent, generic manufacturers are free to launch generic version of the off-patented drug and with the entry of generic versions the price of the branded drug inevitably falls. The huge differences in the price of the generics and the branded drug encourage consumers to shift to the cheaper and widely available generic versions.

Example: In January 2002, when Glucophage (oral antibiotic), went off-patent, within two months approximately 80% of prescriptions prescribed the generic version which rose to 90% within the next six months [3].

Innovator company

Innovator drug companies pour huge amounts of money in drug Research and Development.

Only four to five molecules screened out of thousands reach the clinical trial and out of these only one molecule is finally approved for marketing by the regulatory body. With such low probabilities, it is reasonable for innovators to look out alternatives in order to recover the costs incurred by them during the research and development and regulatory approval of the drug. Although there are provisions in patent laws that are specifically enacted to provide innovators sufficient exclusivity period to enjoy the monopoly but with time and with the rise in the number of generic drugs industries such attempts to exploit the loopholes in the regulatory laws to extend the monopoly over the market have become more aggressive. Ever-greening may seem lucrative but it can also bounce back and produce results opposite to that desired by the company. Consider a case where an innovator company desires to extend the patent term through by obtaining patent on successor drugs; the company incurs substantial costs even though the successor product is just a minor modification of the parent product, and if the successor drug fails to show any improvement in the known efficacy the company will bear heavy loss.

Example: Schering-Plough owned a patent for Claritin, just before the drug went off patent, Schering-Plough in 2002, launched Clarinex

as successor drug to replace Claritin. Due to delay in FDA approval for Clarinex, generic manufacturers got the opportunity to launch the generic versions of Claritin and as a result when Clarinex got approved, Schering-Plough was unable to attract consumers for the successor drug Clarinex. Schering-Plough faced double disappointment as they invested huge amounts in the research and development of Clarinex [3].

Generic drug companies

Since the generic company has to spend less on Research and Development, they are able to provide drugs at prices manifold lower than branded drugs. Consequently, the generics significantly reduce the market share of the branded drugs, which compels the innovator firms to adopt unethical practices of ever-greening. Generic drug companies play a very important role as cheaper generic versions of the costly branded drugs are the only hope to save lives in under-developed and developing countries. Innovator firms exploit the loopholes in the patent laws to acquire additional patents over the parent patent to retain its exclusivity in the market. Thus, these additional patents for trivial modifications fortify the parent patent and significantly delay the entry of generic competitors which in turn directly affects public health.

The consumer

The consumer appears to be the biggest loser in the battle of pricing between the branded drug and the generic drug manufacturers. Entry of 5-6 generic companies in the market lowers the price of the drug up to 70-80% which ultimately benefits the consumer, whereas if the generic drug entry is thwarted, the patient is left with no choice but to buy the highly priced branded drug. Thus, when an innovator firms files and obtains patent over minor modifications for the so called improved successor drugs and obtains extended periods of exclusivity, the launch of generics is delayed and great injustice is done to patients since they could have opted for cheaper generic versions [3].

Provisions in USA, European Union, India and Other Countries to Prevent Ever-greening

United States of America

In USA the Hatch-Waxman Act (Patent Term Restoration Act) of 1984 was enacted to create a balance between the generic and brand drug industry through certain provisions useful for both the generic manufacturer and the innovator companies. The act includes a provision to reward a generic manufacturer who first challenges the innovator's patent.

The first generic applicant, if successful in challenging a patent is rewarded with a 180-day exclusivity period, which provides generic manufacturer an opportunity to exclusively market its products. The 180 days exclusivity period is in recognition of the public interest in encouraging generic manufacturers to launch generic versions of the branded drug and to challenge bogus and stall undue monopolies enjoyed through bogus patents.

Through the Hatch-Waxman Act, 1984 introduced a new procedure under which an ANDA application (Abbreviated New Drug Application) can be filed by the by generic drug manufacturer to the US Food and Drug Administration (FDA) looking for marketing authorisations for the generic versions.

The underlying fact behind the scheme is that if the innovator drug is already approved then, to obtain market authorisation and to launch its generic version, a generic company is required to demonstrate an identical biological effect rather than repeating clinical trials all over again. To balance the interests of the innovator companies, the act requires generic applicant to choose one of the four certifications in relation to the patent status of the competing generic drug:

- Para I: Drug is not patented;
- Para II: Drug patent have expired;
- Para III: Patent will expire by the time the generics drug hits the market;
- Para IV: Patent won't be infringed or the patent is invalid [13].

European Union

In European Union the patent laws are still too lenient and there are not much laws concerning ever-greening, however ever-greening in European Union is considered as the abuse of dominant position and is counted under the scope of Article 102 from the Treaty on the Functioning of the European Union (TFEU). The consideration of ever-greening under Article 102 is still uncertain as it lacks clarity between the lawful and unlawful abuse of the abuse of the dominant position in relation to ever-greening as patent laws being specific to a country therefore a community law such as the Article 102 cannot challenge a country's patent law, this is the major allegation made by those convicted of the abuse of dominant position.

More over patent is an exclusive right granted to the patentee and the patentee has the right to exploit the patent for monopoly so this does not necessarily count as the abuse of dominant position. Ever-greening seems to be forced fit into the scope of article 102, so this article needs a narrow and clear definition to fit ever-greening since the present definition is too broad and the exploitation of the provision seems inevitable [14].

India

Data exclusivity and patent term extension: India has seen a strong lobby against inclusion of data exclusivity provisions for pharmaceuticals, pharmaceuticals and agro-chemicals sectors are deprived of data exclusivity provisions since it is believed to be in the interest of the flourishing generic industry, inclusion of such provisions will have a huge impact on the generic industry and will result in the delayed entry of cheaper versions of branded drugs. Inclusion of the data exclusivity provision in the Indian IP regime will also bring with it the concept of patent term extension.

India introduced product patents for pharmaceuticals in 1995 by signing the TRIPS agreement and as a part of its TRIPS and WTO and commitments amended its Patent Act in three phases in 1999, 2002 and 2005. With the 2005, India introduced new patentability standards which were further restricted by the inclusion of a unique provision, Section 3(d). Under this new provision, new forms of already known substances were not granted a patent unless they are proved to have enhanced the known efficacy of that already known substance.

The statutory intent behind inducting section 3(d) was to curb the unethical practices of ever-greening. Section 3(d) restricts the patentability of certain new forms of older substances unless they satisfy the requirement of enhanced efficacy criteria. Hence, Section 3(d) laid down higher patentability standards for new forms of already known substances and has proved as an effective provision in checking

the unethical practices followed by innovators to extend the patent term [1].

Section 3(d) states:

"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, machine or apparatus unless such known process results in a new product or employs at least one new reactant".

The Novartis vs. Union of India case study: Just one year after its induction into the Indian Patent Act, Section 3(d) came to test. In 2006, Novartis patent application for beta crystalline form of imatinib mesylate was rejected by the Madras Patent Office. The patent office decision was based on the fact that imatinib mesylate (which was a pre 1990s molecule) was a known compound and the beta crystalline form was just a derivative of imatinib mesylate. Novartis even failed to show proof to support its claim of enhanced efficacy over the parent compound, hence, the application by Novartis failed to pass the patentability standards laid down by Section 3(d). Novartis hoping for reversal of the decision, appealed against the decision of patent office to IPAB (Intellectual Property Appellate Board), and alleged that the Section 3(d) is constitutionally invalid and against the terms of TRIPS. Court decided to deal only with the constitutional validity issue and left the issue of TRIPS compatibility issue to the dispute settlement body of the WTO citing that it court lacked jurisdiction over the issue. Court upheld the constitutional validity of Section 3(d) and on TRIPS compatibility the court said that Section 3(d) was crafted utilising the flexibilities offered by the TRIPS framework. IPAB upheld the Madras High Court's decision that the beta crystalline form of imatinib mesylate may be considered novel and inventive but failed to demonstrate enhanced efficacy over imatinib mesylate and hence cannot be granted a patent. Novartis appealed before the Indian Supreme Court against the IPAB decision. The Supreme Court upheld the Madras High Court decision and agreed with the IPAB ruling that Novartis failed to show enhanced therapeutic efficacy over the parent compound, and hence failed to pass the test laid down by Section 3(d). The Indian Supreme Court further held that the enhanced efficacy standard is as per the flexibilities offered by TRIPS framework [15].

Other countries

India's measure to redefine and redesign patent laws received strict opposition from the United States and the European Union. While on the other hand, countries like Argentina, Philippines, Brazil, China, Indonesia, Malaysia, Thailand and South Africa have either emulated or strongly favoured following India's path. India's patent reforms had a remarkable extraterritorial impact. Moreover, others countries are closely monitoring the Indian stand on utilising the flexibilities offered by the Trade Related aspects of Intellectual Property Rights (TRIPS) framework [16].

The Philippines: The Philippines Congress in 1997 enacted a law, known as Republic Act 8293, which aimed at prescribing a TRIPS compliant IPR law. In 2008, Section 22 of this act was amended by the country's congress; the section lists conditions for non-patentable inventions as:

"In the case of drugs and medicines, the mere discovery of a new form or new property 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 the mere use of a known process (is non-patentable) unless such known process results in a new product that employs at least one new reactant".

The amended Section 22 of the Republic Act 8293 incorporates the same language as that of Section 3(d) into the patent law of the Philippines. The Section 22 was adopted by the Philippines government in an effort to increase availability of cheaper drugs its population which comprises of a large low income class [15].

Argentina: In Argentina three joint resolutions were published in May 2012 by Ministry of Health, Ministry of Industry and National Institute for Industrial Property, which revised and restricted the patentability of derivatives of pharmaceutical products. The resolutions were applied to all the pending and future patent applications. Argentina's joint resolutions are considered even stricter than India's Section 3(d) in the sense that they preclude Innovator firms from patenting different attributes of the same drug [15].

Brazil: Recently new guidelines were drafted by the Brazilian Patent Office to restrict the patentability of new forms of already known compounds (polymorphs) or new property or new use of a known process which makes exactly similar sense as that Section 3(d).

Japan: Japan's new patent legislation mentions the subject matter as the new use of a drug can be patented only if the usage is absolutely novel and its use must be clearly differentiated over the original drug.

Mexico: Mexico IP law in Article 19 (Mexican Industrial Property Law, 1991) mentions the same language as that of Section 3(d).

European Patent Office also prescribed new guidelines regarding patentability of polymorphs. For the polymorphs to be considered as inventive the patentee needs to produce data regarding extraordinary technical effect compared to already known compound [17].

Conclusion

Since drug development involves a lot of unknown risks and behind every successful drug molecule there is an extensive research and development which consumes several years, patent clock starts much early in drug development. Most of the countries provide a 20-year exclusivity for a patented drug, considerable amount of this time is lost during the regulatory application and approval process, so it is natural for any innovator firm to resort to undue practices such as ever-greening so as to recover the heavy costs incurred by them, but with time these practices have become too aggressive, Corporate firms are not in any way humanitarian in their approach, even though they pose to be, their sole motive is to maintain their monopoly by increasing number of patents in their patent portfolios. To check this practice some countries have included certain provisions in their patent laws to extend the overall life of the patent so as to recover some of the time lost during regulatory processes, but in turn innovators firms have found loopholes in laws and even started exploiting these official provisions.

In developed countries like USA and that of the European Union the patent laws are too lenient to check ever-greening practices, while, with the Novartis case India gave a clear and strong indication that it would not risk life of poor patients and the public health by permitting ever-greening of drug patents. The judgment in Novartis case also gave a strong message to the world and the innovator firms that India will provide extended market monopoly to pharmaceutical companies only

if a medicine is genuinely shown to be innovative and there is a significant enhancement in the efficacy.

The decision prevents the attempts of pharmaceutical companies who wish to seek ever-greening of patents in India by filing patent on different attributes of the same drug to enjoy extended monopoly and delay of the availability of cheap generic versions. This would certainly facilitate early entry of generic medicines into the market and the impact would be felt not only in India but also across other countries that depend on Indian generic medicines.

Consequentially, threats and veiled attacks are mounted on the Indian Patent system by United States and European Union to remove Section 3(d); United States even classified India as a 'Priority Foreign Country' a tag that is generally given to the worst intellectual property offenders.

Argentina and the Philippines amendments can be seen as a sign that India's Section 3(d) wave is spreading to other parts of the world especially among the developing countries. Patents are considered to present one of the biggest barriers in the access to lifesaving medicines. There is a growing concern that patent protection for pharmaceutical products can limit the lifesaving medicines beyond the reach of large section of the world population. Despite the different types of remedies that are available, the strongest response to the issue of ever-greening can only be made available by availing the flexibilities offered by the patent system.

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