

Anti Pharmaceutical Patent Ever-greening Law: Global Need in Support of Public Health

Say-yed Hesameddin Tafreshi[†]

Vaccine R&D Unit, Research and Production Complex, Pasteur Institute of Iran, Alborz, Iran

Received: 5 June 2019; accepted: 14 August 2019

Drug patenting would be an effective tool to encourage introducing new drugs for prevention and treatment of diseases. The main goal of drug patenting is to protect all the interests of inventor and try to create a secure and confident way to encourage those who are involved in pharmaceutical industries. However, some pharmaceutical companies by using different strategies like, combination, finding new medical use, new formulation or slight changes in old drugs, abuse this tool to extend their patents (patent ever-greening) and obtain more economic advantages. These types of drugs, due to lack of full requirements of an invention such as novelty and inventive step, cannot be considered as new drugs, therefore, cannot be patented. Pharmaceutical patent ever-greening is in contradicted with the spirit of the innovation, invention and commercialization. By preventing the introduction of generic drugs into the market, it might endanger public health *via* continue selling of brand drugs with exorbitant prices. Pharmaceutical patent ever-greening is a global issue because practical approaches to patent ever-greening are currently seen in both developing and developed countries and it imposes a substantial burden on the public health. For this reason, passing a law to ban ever-greening of pharmaceutical patents is essential in all countries of in the world.

Keywords: TRIPS Agreement, US Food and Drug Administration, WHO Essential Medicines List, public health, patent, ever-greening, drug modification, combined drugs, fixed-dose combinations, direct-to-consumer advertising

Despite the presence of the United Nations Charter (1945), the Universal Declaration of Human Rights (1948) and the Constitution of World Health Organization (1948) at global level and many similar rights at regional and national levels, according to the report of the United Nations Secretary General in 2016, due to rising costs and prices of health technologies, millions of people in all countries don't have access to many medicines, diagnostics, medical devices and vaccines.¹

Restriction and lack of access to essential drugs is a global issue² and accordingly the use of generic drugs has become a global need. The use of generic drugs has direct effect on cost savings and these savings can be massive for health care systems. For example, even in relatively rich nations such as the USA, it has saved more than US\$ 1.2 trillion to the US health care system between 2003 and 2012.³ Also, European Commission in 2009 estimated that taxpayers in European countries lost over €3 billion (US\$ 3.4 billion) per year due to postponing of generic drugs production (the findings were confirmed by a 2014 study).⁴

Pharmaceutical Patent Ever-greening (PPE) virtually is a set of various legal, business and technological ways and strategies which are used by pharmaceutical patent owners in order to extend their patents. Some of these strategies include: pay-for-delay settlement, switching to over the counter (OTC), partnerships with generic manufacturers or establishment of generic units. But, the most affordable and used strategy is intentional minor modifications of old drugs in order to obtain multiple patents on the same drug and accordingly earn more economic advantages.⁵ There are several strategies for ever-greening of drug patents, but the main purpose of the present study is especially to investigate the patentability of controversial seven major categories of pharmaceutical products including: enantiomers, combination drugs, new medical uses, new formulations, metabolites, new routes of administration and polymorphs of existing drugs. This study tries to answer the questions; Can a minor modification of an old drug change it to a new drug?; Are these types of drugs fully compliant with the patent requirements?

[†]Email: tafreshih@yahoo.com

Patent

World Intellectual Property Organization (WIPO) defines patent as: "*A patent is an exclusive right granted for an invention, which is a product or a process that provides, in general, a new way of doing something, or offers a new technical solution to a problem*". The patent right is territorial and the exclusive right is granted to a patent owner for generally 20 years from the filing date in accordance with the laws and regulations of the particular country or region that patent owner issues the patent.⁶ That means, there is not a single patent law all over the world and each country can establish a patent law in accordance with its own conditions. Also, by expiring a patent, the protection will be finished and patent holder has not any right to keep this interest and at this stage, the public can be benefited from production of generic drugs. Requirements of an invention in order to get a patent are:

- (i) Novelty: In patent law, novelty is a part of the legal test to ensure that the invention has not been available to the public by any means before the filing date. The goal of the novelty requirement is to avoid double or multiple patents for the same or similar inventions.
- (ii) Inventive step (non-obviousness): Seeking problem-solution approach in order to distinguish, if an invention is new or it is obvious to a skilled person in the art.
- (iii) Industrial applicability (utility) and sufficient disclosure: An invention shall be taken to be capable of industrial application, if it can be made or used in any kind of industry. Also, an inventor must describe the invention to the public in such full and complete details to enable a person with common skills in the art to make and use the invention.⁷

Originator and Generic Drug Manufacturers

Nowadays, producing medicine in the world has been generally recognized under two different methods. (i) Production of a new medicine based on new research and development (R&D), patenting it under patent laws and keeps the exclusive right for originator manufacturer (patent holder) for a certain period of time (20 years) and with a brand name will be sold out. (ii) Production of medicine when the drug patent expired and no more protection vested in inventor or exclusive right has no more effect; thus generic medicines by generic manufacturers will be produced and marketed.⁸

In comparison with brand drugs, generic drugs have much less expensive price (20-90% cheaper than branded drugs) and accordingly playing a vital role in supplying essential drugs especially in low and middle income countries.⁸⁻⁹ There is a big challenge between these two types of drug manufacturers. Originator manufacturers try to grant their inventions as patents and by using different methods attempt to prolong the protection time of these patents exclusively. In contrast, generic manufacturers as a competitor try to examine the licenses of originator companies precisely and if these patent registrations have no consistency with law and regulations of the litigation of the countries, demanding to repeal the execution of the patent protection. Also, they always impatiently waiting to expire the protection time of patents and produce generic drugs. In the following section, some of the methods which are used by originator manufacturers to prolong drug patents, have been discussed.

Enantiomers

Because of high cost of introducing new drugs into the market, originator pharmaceutical companies pursue to introduce and patent enantiomer drugs. The policy is followed just to get benefit from new patent interests again. For example, Prilosec[®] (omeprazole) and Nexium[®] (esomeprazole) are two drugs that being used to control gastric hyperacidity. They both belong to a class of medications, called proton pump inhibitors (PPIs) which work by decreasing the secretion of acid in stomach. When Prilosec[®]'s patent has been expired, Astra Zeneca company introduced a drug named Nexium[®] in 2001 and has been benefited a big financial gain only in this year (\$623 million).¹⁰⁻¹¹

The difference between two drugs is that Prilosec[®] is an equal (racemic) mixture of R- and S-enantiomers but Nexium[®] only consists of S-enantiomer. In other words, they are two isomers of one drug and they are only mirror images of each other. Simply, Nexium[®] is Prilosec[®] without R-enantiomer.

Later, some studies have shown that Nexium[®] has no superior efficacy over prilosec[®].¹²⁻¹³ Based on patent laws and regulations, originator manufacturers should never ever been able to patent a drug twice with the same active ingredient but Astra Zeneca has done it and prevented generic production of the drug. On the other hand, different studies have revealed that single enantiomer drugs had not any superiority over the racemic old drugs and in some cases, undesirable

effects have also observed in comparison with racemic old drugs. Some of the FDA approved medications that have been studied, include: dexlansoprazole, levoleucovorin, levocetirizine, armodafinil, arformoterol, eszopiclone, escitalopram, dexamethylphenidate, and esomeprazole. Between 2001 and 2011, these drugs have been imposed US\$6.3 billion on the US Medicaid programs.¹⁴⁻¹⁵

Combination of Existing Drugs

Combined drugs or fixed-dose combinations (FDCs) are the result of putting two or more medicines together in a single dosage form to treat a single disease (such as, cancer or diabetes) or two closely related diseases (such as, hyperlipidemia and hypertension). It is claimed that combined drugs have the following benefits: overall lower costs in comparison to multiple and separate drugs, improving patient compliance and having higher efficacy with lower risk of adverse reactions.¹⁶⁻¹⁷ However, are these all the facts?

Combined Drugs and Side Effects

Combination of clopidogrel with aspirin can reduce the risk of cardiovascular events but it is associated with increasing risk of bleeding in comparison with aspirin alone.¹⁸

Combined Drugs and Lower Cost

In paper published in Medical Journal of Australia, Australian researchers found that maybe combined drugs are initially cheaper than individual therapies, but more costs are totally paid by the government and the payers. It is worth mentioning that Australia is spending US \$ 600 million per year for heart diseases and diabetes combination therapies.¹⁹

Combined Drugs and Higher Efficacy

Combined drugs do not necessarily have a higher efficacy than separate drugs. For example, the results of a meta-analysis indicated that combined antihypertensive drugs don't have any advantage in blood pressure control and reduction of adverse effects.²⁰ A comparison of antihypertensive drugs, telmisartan and S-amlodipine, resulted the same efficacy and safety for both combined and separate administration of these drugs.²¹ Also, unapproved formulations of antibiotic combined drugs and accordingly rising antimicrobial resistance and health crisis have been reported by Indian researchers.²² Evaluation the safety and rationale use of antibacterial combined drugs in the private sector of eight Latin

American countries (Argentina, Brazil, Chile, Colombia, Mexico, Peru, Uruguay and Venezuela) between 1999 and 2009 showed that the majority of these combined drugs didn't have therapeutic effects.²³ The results of 13 randomized controlled trials analysis from 1987 to 2015 on efficacy, safety and acceptability (including treatment failure, relapse of the disease, death, serious adverse events and adverse events that led to discontinuation of therapy) of anti tuberculosis drugs in both separate and combined forms revealed similar effects for treatment of newly diagnosed pulmonary tuberculosis.²⁴ Even researchers being aware that combined drugs should be only prescribed after treatment failure with separate drugs, cautious is required especially in elderly patients who are suffering from multiple concurrent diseases and regular reassessment of these drugs is urged.²⁵

Combined drugs have some disadvantages include: lack of dose flexibility, enhanced drug interactions between drugs and excipients, difficult in identifying of causative drug(s) responsible for side effects and boost of toxicity.²⁶⁻²⁸

New Medical Uses of Old Drugs

New medical use or drug repositioning (drug repurposing, drug retasking, drug rescuing, therapeutic switching, drug recycling or drug reprofiling) is the use of old drugs for new medical indications (to treat another disease). Drug repositioning is an efficient approach, in order to save money, time and maximize financial return of initial investment, because many existing drugs have: 1) determined formulations and established manufacturing processes, 2) extensive data about absorption, distribution, metabolism, excretion and toxicity, 3) passed clinical trials and less likely to fail future clinical trials because of side effects and 4) post marketing surveillance safety data.²⁹⁻³⁰ Drug repurposing extends to all areas of medicine and there are many examples. Table 1 shows some examples of repositioned drugs.

Even withdrawn drugs (due to safety considerations) reappear in drug repositioning. Thalidomide, which was initially developed as a sedative and then used as a treatment for nausea and vomiting of pregnancy, caused over 10,000 of severe birth defects (phocomelia) in children between 1957 and 1962.³¹ It was withdrawn due to phocomelia, but it was approved by the US Food and Drug Administration (FDA) for treatment of leprosy complications and multiple myeloma (bone marrow

Table 1 — Repositioned drugs for new medical indications

Drug (Generic name)	Original indication	New indication (Brand name)
Acetyl salicylic acid (ASA)	Pain, Inflammation and Fever	Antiplatelet (Aspirin [®])
Minoxidil	Hypertension	Hair loss (Rogaine [®])
Sildenafil	Hypertension	Erectile dysfunction (Viagra [®]), Pulmonary hypertension (Revatio [®])
Finasteride	Prostate hyperplasia	Hair loss (Propecia [®])
Raloxifene	Cancer	Osteoporosis (Evista [®])
Methotrexate	Cancer	Psoriasis, Rheumatoid arthritis (Rasuvo [®] , Trexall [™] , Otrexup [™])
Duloxetine	Depression	Chronic pain disorders (Cymbalta [®] , Irenka [™])

cancer).³² It is currently used for treatments of different diseases including: leprosy, multiple myeloma, Crohn's disease, Behcet's disease, HIV and lupus. Tragically, after the thalidomide disaster in the late 1950s and the early 1960s, the similar event has occurred again in a few Brazilian children due to leprosy treatment of their mothers (who are not informed of the dangers of the drug) with thalidomide.³¹

New Formulations of Old Drugs

Venlafaxine (an antidepressant drug and marketed as Effexor[®]) is an immediate release tablet and due to short half life, generally prescribed in two or three times daily. It found out to cause side effects (nausea and dizziness). However, when the drug will be provided in extended release form (Effexor XR[®]), it is gradually released in the body and would be taken once daily and consequently, reducing side effects.³³⁻³⁴

But efficacy and tolerability of extended release (XR) formulation of venlafaxine is a subject of controversy. For example, the results of two studies demonstrated that extended release formulation of venlafaxine is effective and well tolerated³⁵⁻³⁶, but with respect to antidepressant efficacy, the extended release formulation was equivalent to the immediate release formulation according to a comparative analysis study.³⁷ Venlafaxine XR was recommended for suspension by the Committee for Medicinal Products for Human Use (CHMP) on 21 May 2015 and has been banned in some European countries such as Germany, Malta, Poland, Portugal, the Netherlands and the United Kingdom.³⁸

There are other examples. Extended release formulation of antidepressant drug Prozac[®] and anti-diabetic drug Glucophage[®] entered into the pharmaceutical market by Lilly and Bristol-Myers Squibb respectively when they faced the expiration of their patents for Prozac[®] and Glucophage[®].

Metabolite of Old Drugs

Venlafaxine is extensively metabolized to an active metabolite, O-desmethylvenlafaxine or

briefly desvenlafaxine by the liver. This means, if you take venlafaxine, your body breaks it down into desvenlafaxine. Definitely, venlafaxine is the origin and source of desvenlafaxine and both compounds are closely related to each other.³³ Desvenlafaxine has no additional benefits for patients and in comparison to venlafaxine XR, both drugs have the same pharmacologic and pharmacokinetic profiles. Also, both drugs have shown the similar side effects and tolerability in clinical trials. But, the only significant difference between these drugs, is the price (US \$ 2,000 yearly for brand name of desvenlafaxine and US \$150 yearly for generic venlafaxine XR, based on average wholesale price).³⁹⁻⁴¹ Prescription of Pristiq[®] (desvenlafaxine) instead of off-patent Effexor XR[®], costs more than A\$21 million per year to Australian taxpayers based on reports of prescription volumes in 2013-2014.⁴¹

Desvenlafaxine is marketed as Pristiq[®] by Pfizer. Effexor XR[®] and Pristiq[®] extend the life of Effexor[®] patent. It is important to note, there is not any generic version of Pristiq[®] until August of 2023, when the Pristiq[®] patent expires.⁴¹

New Routes of Administration for Old Drugs

Imitrex[®] (Sumatriptan, a migraine drug), originally formulated in tablet form and for oral administration. Then it was reformulated, patented and obtained the FDA approval for intranasal delivery (nasal administration) by GlaxoSmithKline (GSK). The original patent of the drug expired in 2006, but the company extended its patent protection time until February of 2009 by presentation of nasal spray of the drug. The drug faced worldwide total sales of over US\$1 billion in 2006 for GSK.⁴²

Polymorphs

The term of "polymorphism" is applied in different fields such as Biology, Computer Science and Medicine, but what is the definition of polymorphism in chemistry? Simply, polymorphism is the existence of different kinds of crystal structure of the same

chemical compound and each of these crystalline structures, is called polymorph. Polymorphs have different physical and chemical properties. For instance, diamond and graphite, both are made of pure carbon, but their physical and chemical properties are different drastically.⁴³ In pharmaceutical industries, polymorphism of an active pharmaceutical ingredient (API) and accordingly its physical and chemical properties, is critical for successful drug development and significantly affects on variety of API properties, including production of API, flowability, tableting, dissolution rate, solubility, stability and even efficacy and toxicity.⁴⁴

But what would be the other side of the coin? It should be noted that change in polymorphism is not necessarily associated with enhancement of drug efficacy. For example, a more stable polymorph of a drug may enhance the expiration date of the drug or greater tensile strength of Sulfamerazine form-I polymorph tends to better tablet ability and compressibility.⁴⁴⁻⁴⁵ Also, approximately 51% of the new molecular entities approved by the FDA between 1985-2005 with at least one patent, have claims to polymorphs, isomers, pro-drugs, esters or salts. Interestingly, independent secondary patents (patents with only secondary claims and no chemical compound claims) on polymorphs, isomers, pro-drug, ester, and/or salt claims add an average of 6.3 years (5.3 to 7.3 years) of patent life.⁴⁶ Through, the strategy of polymorphs patenting and in the example of atorvastatin, Pfizer extended market exclusivity of the drug for additional 6 years (from 2011 to 2017) by disclosing the drug new polymorphs as a separate patent or in the case of lumacaftor, Vertex Pharmaceuticals increased patent life of the drug for additional 4 years (from 2026 to 2030) by holding 14 patents with a polymorph patent.⁴⁵

Efficacy, Toxicity and Price of New Drugs

Sometimes, it is claimed that these types of drugs are more efficient, less toxic and have less price in comparison with original ones. According to the WHO Report, drugs that being categorized as a low or without efficacy by the FDA, have approximately the same price of the original drugs in the USA and even double price of original drugs in Sweden. Cockburn and Anis compared the price of anti-arthritis drugs just based on their toxicity and efficacy in 1998. The result was vice-versa, by increasing price, their efficacy were decreased and their toxicity were increased.⁴⁷

According to the 2016 annual report, even a successful country at controlling the price of patented drugs such as Canada, after the United States and Switzerland, is the third highest priced country among Organization for Economic Cooperation and Development (OECD) countries.⁴⁸ Therefore, introduction of new patented drugs, does not necessarily mean that they are more efficient, less toxic and cheaper than original ones.

TRIPS and Drug Patenting

Before the adoption of World Trade Organization (WTO) Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS) in 1994, over 50 countries in the world did not support drug patenting; so many other countries only supported the process of producing medicines, but not new drugs.⁴⁹⁻⁵⁰ All these demarcations and limitations were only to keep the price of drugs down and let the generic manufacturers to produce and supply of essential drugs in order to support of public health.

Over 15 years, after development and release of the WHO Essential Medicines List and supporting generic drugs production in the developing countries, TRIPS Agreement, partially under pressure from the USA, was adopted in 1994 and came into effect in January 1995.³ Interestingly, TRIPS is administered by the WTO and not by the WIPO. TRIPS invokes so many laws and regulations for the first time in regards of drug patenting, such as, prohibition of excluding of drug patenting and executing the protection time of patents for 20 years. Even, TRIPS-plus standards provide stronger support for intellectual property rights. The results of these standards is increasing in economic benefits of the patent holders and decreasing in public access to knowledge and technology.⁵¹

It is claimed that TRIPS flexibilities (two of the most important ones, compulsory licensing and parallel importation) and the Declaration on TRIPS and Public Health signed in Doha in 2001 (the Doha Declaration) provide access to medicines and reinforce to promote public health solutions in developing countries, respectively. However, are these flexibilities practical?

Compulsory Licensing

Paragraph (f) under Article 31 of the TRIPS Agreement specifies that: *“any such use shall be authorized predominantly for the supply of the domestic market of the Member authorizing*

such use".⁵² Implementation of compulsory licensing in the developing countries is very difficult because this flexibility is considered to supply of drugs for the domestic market and these countries don't have realistically a suitable and strong pharmaceutical industrial infrastructure. On the other hand, according to the Paragraph (b) of the Article and in the best situation, compulsory licensing is practical in situations of national emergency (without authorization from the right holder) and it is unusable for routine supply of essential and expensive drugs. Also, adequate compensation must be paid to the patent holder in the event of compulsory licensing.⁵²⁻⁵⁵

Parallel Importing

Parallel imports involve the import and resale of goods at a cheaper price from another country without the express permission of the right holder. But, there are barriers to parallel importing despite the promise of the Article 6 and the reaffirmations provided by the Doha Declaration, such as, economical and political pressure and fear of incurring in other trade areas due to powerful trading partners; ⁵⁶⁻⁵⁷ economic retaliatory actions of big economical powers against developing countries (threat to trade sanctions of South Africa by the United States in 1997 in order to repeal a section of the Medicines and Related Substances Control Amendment Act which allowed compulsory licensing and parallel importing in spite of compliance with the TRIPS Agreement);⁵³ insufficient demand; difficulties in generic drugs registration; undermining the Doha Declaration and the Paragraph; Decision by enhancement of intellectual property protections in regional and bilateral trade agreements such as TRIPS-Plus provisions for medicines; and lack of legislative and regulatory requirements both for importing and exporting in developing countries.⁵⁸

Discussion

From a human health rights perspective, access to drugs and medical devices, are essential in developing countries.^{3,59} Production, import and export of generic drugs due to their cheaper prices, are the center of attention both for health system decision makers and generic manufacturers in all countries of the world especially in developing countries. But, generic drugs cannot be produced prior to patents expiration of brand drugs. On the other hand, monopolism and the exclusive rights of producing, using, selling and

distributing are only granted for patent owners during patent protection period (20 years) and upon expiration of a branded drug's patents, these monopoly and exclusive rights will be disappeared. For this reason, originator manufacturers by using different strategies attempt to keep these exclusive rights, extend the patent life of their drugs (more than 20 years) and continue to prevent or to delay generic manufacturers' entry.

In this paper, review and evaluation of seven different types of drug modifications have shown that in all cases, regardless of their efficacy, toxicity and price, these modified drugs cannot be patented due to lack of novelty and inventive step.⁶⁰ For example, according to the patent definition and requirements of an invention, what is the novelty of enantiomers, drugs metabolites, polymorphs and new routes of administration of old drugs? Isn't it obvious that combination of two anti-hypertensive drugs (of course, if efficacy of the combined drug can be proved by the inventor) provides better blood pressure control than separate ones or an extended release form of a drug provide an initial and then a gradual release of the drug for long periods of time in the body and accordingly reduce dosing frequency of the drug and its side effects? Isn't it obvious that a polymorph with better tensile strength has better tableability or a drug metabolite has a better excretion in the body? Briefly, these minor modified drugs (with minor or no substantive improvements in efficacy) due to lack of full requirements of an invention such as novelty and obviousness cannot be considered as new drugs, therefore, cannot be patented. A fundamental question in this regard is: Can an invention be patented more than once? It depends, from legal and regulatory perspectives, it can't; but, from ever greening perspective, surely yes! Why not?

It is claimed that originator manufacturers use these strategies in order to compensate the high costs of research and development of the new drugs. Because of differences in methods, data sources, time periods and lack of transparency, the actual cost of new drug R&D is unclear. For these reasons, different estimates of developing a new drug from R&D to the market (even more than 9 to 14-fold) from US\$92 million to US\$883.6 million⁶¹ or from US\$204 million⁶² to US\$2870 million⁶³ have been reported by researchers.

Despite wide varieties, not all of the costs involved are not only relevant to the research and development

of new drugs. Drug marketing is a big business and the steep rise in costs of new drug R&D is partially due to drug advertising including: direct-to-consumer (DTC) advertising and physicians' visits. However, advertising is a very influential factor in business of pharmaceutical industry. In the United States, pharmaceutical companies spent nearly 2 times more on marketing than R&D⁶⁴ because for every \$1 invested by the industry in DTC advertising, the market produced a gain of \$4.20.⁶⁵ Figure 1 illustrates annual costs of DTC advertising spent by the US pharmaceutical industries.⁶⁶⁻⁶⁸

Pharmaceutical industries of the United States spent \$12 million in 1980; \$47 million in 1990 and \$340 million in 1995 on DTC advertising (3,000% nearly increased during 15 years). In 1997, when the FDA issued the draft guidance on this topic, the DTC investment tripled to \$1.2 billion in 1998⁶⁶ and reached to \$5 billion in 2017.⁶⁷⁻⁶⁸ The skyrocketing cost of DTC advertising directly affects the drug price. For instance, the cost of Plavix[®] increased (considering Medicaid funds spent for Plavix[®] in pharmacies) due to the need to regain the high costs of DTC advertising.⁶⁹

The originator manufacturers have also not been paid the same R&D costs (and not drug advertising costs) for these minor modifications of existing drugs? For example, AstraZeneca has not been paid the same R&D cost for Nexium[®] as much as paid for Prilosec[®]; similarly, Pfizer has not been paid the same R&D cost for Effexor XR[®] as much as paid for Effexor[®].

Pragmatic approaches to evergreening of patents are now seen in developed, developing and least developed countries.⁷⁰ While there are various regulations in the United States (35 U.S.C 102(b), 35 U.S.C 103(a) and 35 U.S.C 271 (e)) and Europe (Articles 54 and 56 which relate to novelty and inventive step, respectively) that restrict patent evergreening,⁷¹ but many developing countries

including: Chile, South Africa, Brazil, Argentina and India don't have efficient measures in order to prevent pharmaceutical patent evergreening.⁷²⁻⁷⁵ Lack of these measures urges to balance between public health interests and interests of patent owners⁷⁶ and seeking suitable approaches to facilitate better access to drugs in developing countries.⁷⁷ Prevention of pharmaceutical patent evergreening is particularly important for developing and least developed countries. For example, a new study revealed that poor and developing countries pay up to 30 times more for basic medicines (like acetaminophen or omeprazole) than other countries⁷⁸ and average percentage savings of using generic drugs in some countries are very impressive (89% in Colombia and 84% in Indonesia only for 9 medicines).⁷⁹ Of course, some good efforts have been made by some countries to solve pharmaceutical patent evergreening, but these efforts are insufficient. The India's 3(d) Section of the Patents Act is a good model and example.

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. Explanation: "Salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations, and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy"*.

According to the Section 3(d) of the Patents Act, new forms of salts, esters, polymorphs, metabolites, change in particles size of drugs, difference in isomerism, isomers mixture, complex formation, combination of drugs and drug derivatives, do not consider as new drugs and cannot be patented, unless a significant change on the therapeutic properties of drugs has been occurred or these changes directly affect a great deal on the "efficacy" of the drugs. Such a law and regulation is helpful, but it would not be enough for supporting of public health in developing countries, because efficacy is not a quantified value and there is not any numerical standard for expression of efficacy. Therefore, lack of clarification and the scope definition of "enhanced efficacy" are entirely apparent. On the other hand, due to complexity of pharmaceutical technologies (process) and drug

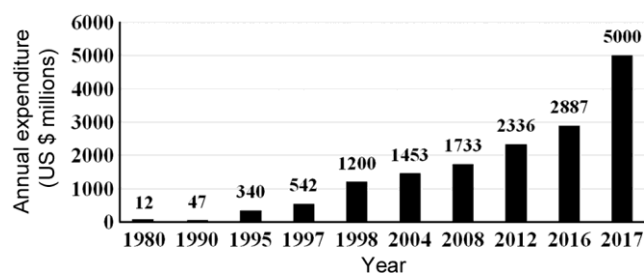


Fig. 1 — Costs of DTC advertising in the United States, 1980-2017

formulations (product); it may not be very difficult to prove efficacy enhancement of new formulations of existing drugs.⁸⁰⁻⁸² Thus, in addition to avoid using these arguable and misinterpretable terms, all terms and conditions must be carefully defined and clarified in the laws and regulations of the Patents Act in all countries of the world.

Unfortunately, from the perspective of international flexibilities, it seems the system under the Paragraph 6 of the Decision has not appropriate legal capacity for providing essential medicines and supporting public health and not only it is improbable to play a role in regulating of the drugs prices and incentives to invest on production of vital drugs, but also legally permits patent owners to prevent access to their patented drugs even in the case of compelling humanitarian reasons.⁸³

Conclusion

A plenty of money is being paid by health systems of both developing and developed countries for the delay market entry of generic drugs. For this reason, PPE is the issue of global and accordingly, needs global solutions. But before any international action, because of territorial nature of patent exclusive rights, the easiest ways to fight PPE are: Exact examination of drug patent applications by health care professionals and examiners of patent office and establishment a close and effective relationship between these organizations in each country in order to support and promote of public health; Implementing the necessary amendments of the Patents Act in all countries in order to support of public health and; and Passing a law on prevention of PPE by legislatures in all countries. Such a law must be comprehensive and should be full extent, so that not only prevent all kinds of PPE including minor modifications of existing drugs, but also considers them unlawful and subjects to prosecute and heavy punishment due to endangering of public health. For example, for every attempt to PPE, the law provides suspension of one or more recently drug patents, an extra mulct payment or solving a health problem (in that country). At international level, it seems necessary to perform a feasibility study on the establishment of an international organization for examination all health-related patents (medicines, diagnostics, medical devices and vaccines) in order to help those countries that don't have a suitable and efficient patent examination system. To conclude, a twenty-years period is sufficient time for originator

manufacturers' revenue and compensation of R&D costs, advertising costs and even lobbying costs and it will be no longer necessary to extent the patent life or ever-greening of pharmaceuticals.

References

- 1 <http://apps.who.int/medicinedocs/documents/s23068en/s23068en.pdf> (accessed on 3 January 2019).
- 2 Hill A M, Barber M J & Gotham D, Estimated costs of production and potential prices for the WHO Essential Medicines List, *BMJ Global Health*, 3 (2018), e000571. doi:10.1136/bmjgh-2017-000571.
- 3 Danta M & Ghinea N, The complex legal and ethical issues related to generic medications, Viral Hepatitis: A case study, *Journal of Virus Eradication*, 3 (2017) 77-81.
- 4 Wouters O J, Kanavos P G & Mckee A M, Comparing generic drug markets in Europe and the United States: Prices, volumes, and spending, *The Milbank Quarterly*, 95 (2017) 554-601, doi:10.1111/1468-0009.12279.
- 5 Kumar A & Nanda A, Ever-greening in pharmaceuticals: Strategies, consequences and provisions for prevention in USA, EU, India and other countries, *Pharmaceutical Regulatory Affairs*, 6 (2017) 1000185, doi:10.4172/2167-7689.1000185.
- 6 <http://www.wipo.int/patents/en/>, (accessed on 5 January 2019).
- 7 http://www.wipo.int/edocs/mdocs/africa/en/wipo_pat_hre_15/wipo_pat_hre_15_t_3.pdf (accessed on 5 January 2019).
- 8 Dunne S, Shannon B & Dunne C *et al.*, A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study, *BMC Pharmacology and Toxicology*, 14 (2013) 1, doi:10.1186/2050-6511-14-1.
- 9 Midha S, Strategies for drug patent ever-greening in the pharmaceutical industry, *International Journal of Pharmaceutical Sciences and Business Management*, 3 (2015) 11-24.
- 10 Cohn J, The drug price controversy nobody notices, *The Milbank Quarterly*, 94 (2016) 260-26. doi:10.1111/1468-0009.12193.
- 11 Pharma overview, *Chemical & Engineering Weekly Newsletter*, 80 (2002) 39-49. <http://plg-group.com/wp-content/uploads/2014/03/Pharma-Overview-Chemical-Engineering-News-Dec-2002.pdf>, (accessed on 13 January 2019).
- 12 Mahoney S P, Is esomeprazole (Nexium) more effective than omeprazole (Prilosec) in reducing heartburn and in increasing the rate of esophageal healing in adults with endoscopically diagnosed erosive esophagitis (EE)?, *PCOM Physician Assistant Studies Student Scholarship*, Paper: 26 (2011)<https://pdfs.semanticscholar.org/126b/1d98fc5f3b600b5b0f1d059ea053301abe2f.pdf>, (accessed on 13 January 2019).
- 13 Asghar W, Pittman E & Jamali F, Comparative efficacy of esomeprazole and omeprazole: Racemate to single enantiomer switch, *Daru Journal of Pharmaceutical Sciences*, 23 (2015) 50, doi:10.1186/s40199-015-0133-6.
- 14 Gellad W F, Choi P, Mizah M *et al.*, Assessing the chiral switch: Approval and use of single-enantiomer drugs, 2001

- to 2011, *The American Journal of Managed Care*, 20 (2014) 90-97.
- 15 Valentová J & Hutt A J, Chiral switch: Pure enantiomers of drugs instead of racemic mixtures, *Ceská a Slovenská Farmacie*, 53 (2004) 285-293.
 - 16 Shenfield G M, Fixed combination drug therapy, *Drugs*, 23 (1982) 462-480.
 - 17 Bell D S, Combine and conquer: Advantages and disadvantages of fixed-dose combination therapy, *Diabetes, Obesity and Metabolism*, 15 (2013) 291-300, doi: 10.1111/dom.12015.
 - 18 Squizzato A, Bellesini M, Takeda A *et al.*, Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular events, *The Cochrane Database of Systematic Reviews*, 1 (2017) CD005158, doi:10.1002/14651858.CD005158.pub4.
 - 19 Clarke P M & Avery A B, Evaluating the costs and benefits of using combination therapies, *The Medical Journal of Australia*, 200 (2014) 518-520, doi:10.5694/mja14.00199.
 - 20 Gupta A K, Arshad S & Poulter N R, Compliance, safety, and effectiveness of fixed-dose combinations of anti-hypertensive agents: A meta-analysis, *Hypertension*, 55 (2010) 399-407, doi:10.1161/HYPERTENSIONAHA.109.139816.
 - 21 Oh M, Park S E, Ghim J L *et al.*, Comparative pharmacokinetics of a fixed-dose combination vs concomitant administration of telmisartan and S-amlodipine in healthy adult volunteers, *Drug Design, Development and Therapy*, 11 (2017) 3543-3550, doi:10.2147/DDDT.S148534.
 - 22 Mc Gettigan P, Roderick P, Kadam A & Pollock A, Threats to global antimicrobial resistance control: Centrally approved and unapproved antibiotic formulations sold in India, *British Journal of Clinical Pharmacology*, 85 (1) (2019) 59-70, doi:10.1111/bcp.13503.
 - 23 Wirtz VJ, Mol P G, Verdijk J *et al.*, Use of antibacterial fixed-dose combinations in the private sector in eight Latin American countries between 1999 and 2009, *Tropical Medicine & International Health*, 18 (2013) 416-425. doi:10.1111/tmi.12068.
 - 24 Gallardo C R, Rigau C D, Valderrama Rodríguez A *et al.*, Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis, *Cochrane Database of Systematic Reviews*, 5 (2016) CD009913, doi:10.1002/14651858.CD009913.pub2.
 - 25 Bouvenot G, Sassard J & Montastruc J L, For an optimal use of fixed drug combinations, *Therapie*, 72 (2017) 665-668, doi:10.1016/j.therap.2017.07.003.
 - 26 Ugurlu T & Ozaydin T, An overview on fixed dose combinations, *Asian Journal of Pharmaceutical Technology & Innovation*, 2 (2014) 75-81.
 - 27 Gautam C S & Saha L, Fixed dose drug combinations (FDCs): Rational or irrational: A view point, *British Journal of Clinical Pharmacology*, 65 (2008) 795-79, doi:10.1111/j.1365-2125.2007.03089.x.
 - 28 Gupta Y K & Ramachandran S S, Fixed dose drug combinations: Issues and challenges in India, *Indian Journal of Pharmacology*, 48 (2016) 347-349, doi:10.4103/0253-7613.186200.
 - 29 Ashburn T T & Thor K B, Drug repositioning: Identifying and developing new uses for existing drugs, *Nature Reviews Drug Discovery*, 3 (2004) 673-683, doi:10.1038/nrd146.
 - 30 Tobinick E L, The value of drug repositioning in the current pharmaceutical market, *Drug News & Perspectives*, 22 (2009) 119-125, doi:10.1358/dnp.2009.22.2.1343228.
 - 31 Vargesson N, Thalidomide-induced teratogenesis: History and mechanisms, Birth Defects Research Part C, *Embryo Today*, 105 (2015) 140-156, doi:10.1002/bdrc.21096.
 - 32 <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107296.htm> (accessed on 10 February 2019).
 - 33 https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020151s044,020699s071lbl.pdf (accessed on 10 February 2019).
 - 34 Wellington K & Perry C M, Venlafaxine extended-release: A review of its use in the management of major depression, *CNS Drugs*, 15 (2001) 643-669.
 - 35 Wright C W, Aikman M S, Werts E *et al.*, Bioequivalence of single and multiple doses of venlafaxine extended-release tablets and capsules in the fasted and fed states: Four open-label, randomized crossover trials in healthy volunteers, *Clinical Therapeutics*, 31 (2009) 2722-2734, doi:10.1016/j.clinthera.2009.11.025.
 - 36 Cunningham L A, Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression, Venlafaxine XR 208 Study Group, *Annals of Clinical Psychiatry*, 9 (1997) 157-164.
 - 37 Olver J S, Burrows G D & Norman T R, The treatment of depression with different formulations of venlafaxine: A comparative analysis, *Human Psychopharmacology: Clinical and Experimental*, 19 (1) (2004) 9-16, doi:10.1002/hup.551.
 - 38 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/05/WC500187078.pdf (accessed on 17 February 2019).
 - 39 Colvard M D, Key differences between Venlafaxine XR and Desvenlafaxine: An analysis of pharmacokinetic and clinical data, *Mental Health Clinician*, 4 (1) (2014) 35-39, doi:10.9740/mhc.n186977.
 - 40 https://www.cadth.ca/sites/default/files/pdf/htis/2017/RC0921%20Desvenlafaxine_Final.pdf (accessed on 18 February 2019).
 - 41 Gleeson D H, Moir H & Lopert R, Costs to Australian taxpayers of pharmaceutical monopolies and proposals to extend them in the Trans-Pacific Partnership Agreement, *The Medical Journal of Australia*, 202 (2015) 306-308, doi:10.5694/mja14.01682.
 - 42 Gupta H, Kumar S, Roy S K *et al.*, Patent protection strategies, *Journal of Pharmacy & Bioallied Sciences*, 2 (1) (2010) 2-7, doi:10.4103/0975-7406.62694.
 - 43 Brog J P, Chanez C L, Crochet A *et al.*, Polymorphism, what it is and how to identify it: A systematic review, *RSC Advances*, 3 (2013) 16905-16931, doi:10.1039/C3RA41559G.
 - 44 Raza K, Kumar P, Ratan S *et al.*, Polymorphism: The phenomenon affecting the performance of drugs, *SOJ Pharmacy & Pharmaceutical Sciences*, 1 (2014) 10, doi:10.15226/2374-6866/1/2/00111.
 - 45 Tandon R, Tandon N & Kumar Thapar R, Patenting of polymorphs, *Pharmaceutical Patent Analyst*, 7 (2018) 59-63, doi:10.4155/ppa-2017-0039.
 - 46 Kapczynski A, Park C & Sampat B, Polymorphs and prodrugs and salts (Oh My!): An empirical analysis of

- "Secondary" pharmaceutical patents, *PLoS ONE*, 7 (2012) e49470, doi:10.1371/journal.pone.0049470.
- 47 http://www.who.int/intellectualproperty/topics/ip/en/Me-tooDrugs_Hollis1.pdf (accessed on 2 March 2019).
- 48 http://www.pmprbcpmb.gc.ca/CMFiles/Publications/Annual%20Reports/2017/2016_Annual_Report_Final_EN.pdf (accessed on 2 March 2019).
- 49 Nitsan C & Shadlen K C, Intellectual property, access to medicines, and health: New research horizons, *Studies in Comparative International Development*, 50 (2015) 143-156.
- 50 Sterckx S, Patents and access to drugs in developing countries: An ethical analysis, *Developing World Bioethics*, 4 (1) (2004) 58-74.
- 51 Frankel S, Challenging TRIPS-Plus agreements: The potential utility of non-violation disputes, *Journal of International Economic Law*, 12 (2009) 1023-1065, doi:10.1093/jiel/jgp039.
- 52 https://www.wto.org/english/docs_e/legal_e/27-trips.pdf (accessed on 15 March 2019).
- 53 Subhan J, Scrutinized: The TRIPS Agreement and public health, *McGill Journal of Medicine*, 9 (2006) 152-159.
- 54 Hoen E F M, Veraldi J, Toebes B *et al.*, Medicine procurement and the use of flexibilities in the Agreement on Trade-Related Aspects of Intellectual Property Rights, 2001-2016, *Bulletin of the World Health Organization*, 9 (2018) 185-193, doi:10.2471/BLT.17.199364.
- 55 http://unctad.org/en/PublicationsLibrary/ictsd2006ipd17_en.pdf (accessed on 20 March 2019).
- 56 Bradford Kerry V & Lee K, TRIPS, the Doha Declaration and Paragraph 6 Decision: What are the remaining steps for protecting access to medicines? *Global Health*, 3 (2007) 3, doi:10.1186/1744-8603-3-3.
- 57 Cohen J C, Gyansa-Lutterodt M, Torpey K *et al.*, TRIPS, the Doha Declaration and increasing access to medicines: Policy options for Ghana, *Global Health*, 1 (2005) 17, doi:10.1186/1744-8603-1-17.
- 58 https://www.iprsonline.org/resources/docs/Baker_TRIPS_Flex.pdf (accessed on 25 March 2019).
- 59 Oguanobi H L, Broadening the conversation on the TRIPS Agreement: Access to medicines includes addressing access to medical devices, *The Journal of World Intellectual Property*, 21 (2018) 70-87, doi:10.1111/jwip.12091.
- 60 http://www.undp.org/content/dam/undp/library/HIV/AIDS/UNDP_patents_final_web_3.pdf (accessed on 30 March 2019).
- 61 Morgan S, Grootendorst P, Lexchin J *et al.*, The cost of drug development: A systematic review, *Health Policy*, 100 (1) (2011) 4-17, doi:10.1016/j.healthpol.2010.12.002.
- 62 Light D W & Warburton R, Demythologizing the high costs of pharmaceutical research, *BioSocieties*, 6 (1) (2011) 34-35, doi:10.1057/biosoc.2010.40.
- 63 DiMasi J A, Grabowski H G & Hansen R W, Innovation in the pharmaceutical industry: New estimates of R&D costs, *Journal of Health Economics*, 47 (2016) 20-33, doi:10.1016/j.jhealeco.2016.01.012.
- 64 Masood I, Ibrahim M I M, Hassali M A *et al.*, Evolution of marketing techniques, adoption in pharmaceutical industry and related issues: A review, *Journal of Clinical and Diagnostic Research*, 3 (2009) 1942-1952.
- 65 Porter D M, Direct-to-consumer (DTC) pharmaceutical marketing: Impacts and policy implications, *SPNHA Review*, 7 (1) (2011) Article 5.
- 66 Ventola C L, Direct-to-consumer pharmaceutical advertising, Therapeutic or toxic? *P&T*, 36 (10) (2011) 669-674, 681-684.
- 67 Parekh N & Shrank W H, Dangers and opportunities of direct-to-consumer advertising, *Journal of General Internal Medicine*, 33 (2018) 586-587, doi:10.1007/s11606-018-4342-9.
- 68 Schwartz L M & Woloshin S, Medical marketing in the United States, 1997-2016, *The Journal of the American Medical Association*, 321 (1) (2019) 80-96, doi:10.1001/jama.2018.19320.
- 69 Law M R, Soumerai S B, Adams A S *et al.*, Costs and consequences of direct-to-consumer advertising for clopidogrel in Medicaid, *Archives of Internal Medicine*, 169 (2009)1969-1974, doi:10.1001/archinternmed.2009.320.
- 70 Rathod S K, Ever-greening: A status check in selected countries, *Journal of Generic Medicines*, 7 (3) (2010) 227-242, doi:10.2139/ssrn.2691251.
- 71 Bansal I S, Sahu D, Bakshi G & Singh S, Evergreening-A controversial issue in pharma milieu, *Journal of Intellectual Property Rights*, 14 (2009) 299-306.
- 72 Vawda Y A, After the Novartis judgment - 'Evergreening' will never be the same again!, *Law, Democracy and Development*, 18 (2014) 305-316, doi:10.4314/ldd.v18i1.15.
- 73 Abud M J, Hall B & Helmers C, An empirical analysis of primary and secondary pharmaceutical patents in Chile, *PLoS One*, 10 (4) (2015) e0124257, doi:10.1371/journal.pone.0124257.
- 74 Sampat B N & Shadlen K C, The effects of restrictions on secondary pharmaceutical patents: Brazil and India in comparative perspective, <https://pdfs.semanticscholar.org/4527/1e5d7c002400d4e3a8a6baff1fd75a9db583.pdf> (accessed on 15 July 2019).
- 75 Sampat B N & Shadlen K C, Secondary pharmaceutical patenting: A global perspective, *Research Policy*, 46 (3) (2017) 693-707, doi:10.1016/j.respol.2017.01.005.
- 76 Kuan E S, Balancing patents and access to medicine, *Singapore Academy of Law Journal*, 21 (2009) 457-484.
- 77 Stevens H & Huys I, Innovative approaches to increase access to medicines in developing countries, *Frontiers in Medicine*, 4 (2017) 218, doi:10.3389/fmed.2017.00218.
- 78 <https://www.cgdev.org/sites/default/files/better-health-procurement-tackling-triple-transition.pdf> (accessed on 27 July 2019).
- 79 Cameron A, Mantel-Teeuwisse A K, Leufkens H G & Laing R O, Switching from originator brand medicines to generic equivalents in selected developing countries: How much could be saved? *Value in Health*, 15 (5) (2012) 664-673, doi:10.1016/j.jval.2012.04.004.
- 80 Basheer S & Reddy P, The "Efficacy" of Indian patent law: Ironing out the creases in Section 3(d), *Scripted*, 5(2) (2008) 232-266, doi:10.2966/scrip.050208.232.
- 81 Kant A, Section 3(d) new Indian perspective, *Journal of Intellectual Property Rights*, 14 (2009) 385-396.
- 82 Kant A, 'Efficacy' factors under Section 3(d): A 'law and economics' perspective, *Journal of Intellectual Property Rights*, 18 (2013) 212-229.
- 83 Correa C M, TRIPS Agreement and access to drugs in developing countries, *Sur Revista Internacional de Direitos Humanos*, 2 (3) (2005) 26-39, doi:10.1590/S1806-64452005000200003.