

PHARMACEUTICAL PATENTS REVIEW  
RELEVANT MATTERS FOR PUBLIC HEARING  
TUESDAY, 12 FEBRUARY 2013



### Executive Summary

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The phenomenon called evergreening is the end product of a systemic failure in the pharmaceutical patent system. Weak or very low patentability standards, broadening patentability to include methods of medical treatment, poor patent quality, lack of financial incentives to challenge dubious pharma patents, the readiness of courts to enjoin pharma patent challengers, poorly drafted contributory infringement provisions, too much emphasis on the courts to vet the system and the complete absence of criminal and effective civil sanctions against the misuse of the system, have all contributed to the breakdown of the pharmaceutical patent system.

The disparity in government policies relating to pharmaceuticals is the principal cause of this systemic failure. There has been an overemphasis for far too long on meeting the needs and demands of one half of the pharmaceutical industry, namely, branded pharmaceuticals. While it is important to encourage investment in the research and development of new medicines, it is just as important to maintain an appropriate balance within the system so that the other half of the industry, namely the generics industry, is able to provide *timely access for Australians to quality, safe, efficacious and affordable medicines at a cost the PBS and taxpayers can afford.*

A consequence of this systemic failure is a weakening of the generics industry in this country to the point that unless there is immediate action by the Australian Government there will be fewer patent challenges in the future with the result that the cost of medicine to the Commonwealth will be much higher than it otherwise might need to be. Unless the imbalance is redressed, even raising patentability thresholds will not be enough to encourage the generics industry to challenge evergreening patents. And if the generics industry is no longer able to perform this crucial 'checks and balances' role, then the cost of medicine to the PBS will increase.

The following information conclusively and powerfully demonstrates is how the system actually encourages evergreening. It highlights the various weaknesses and provides examples in the context of the system of the consequences to the Commonwealth and to the Australian people.

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## **About Alphapharm**

Alphapharm is Australia's leading supplier by volume of prescription medicines to the Pharmaceutical Benefits Scheme (PBS). One in seven prescriptions for PBS medicines is dispensed with an Alphapharm product. The company specialises in bringing patent-expired medicines to market, which contributes to the sustainability of the PBS by providing timely access to quality, safe, efficacious and affordable medicines. Alphapharm medicines are made to the highest global quality standards and have the same effect on the body as initial brands.

Alphapharm pioneered generic medicines in Australia in 1982 with twelve staff and four products. Today, we have some 600 employees nationally, including 450 at our state-of-the-art manufacturing plant at Carole Park, Queensland. Almost a quarter of Alphapharm's employees focus on the quality assurance and quality control of our products. This year, the plant will produce 3.1 billion doses of which about 1.7 billion will be exported to some 50 countries around the world.

Alphapharm consistently adheres to strict quality control testing and practices throughout its facility ensuring its products meet its established, documented standards for safety and effectiveness.

Alphapharm's quality control labs test and re-test raw materials, in-process products and finished goods for dissolution, potency, content uniformity and stability. The quality assurance team makes certain the company's products are made to the highest global quality standards. This means satisfying Australian, European Union, United Kingdom, United States, Canadian and New Zealand standards of Good Manufacturing Practice (GMP). This is vital to its business, because apart from supplying the Australian market, Alphapharm exports products to more than 50 countries, including to Europe, South East Asia and the U.S. With methodical documentation, ongoing monitoring procedures, and stringent product testing, Alphapharm is ready for inspection 365 days a year. But quality is more than just processes. It depends on the commitment to excellence of Alphapharm employees - a commitment that is demonstrated every day, by every member of the company.

Alphapharm is part of US-based Mylan.

## **About Mylan**

Mylan is a global pharmaceutical company committed to setting new standards in health care. Working together around the world to provide 7 billion people access to high quality medicine, we innovate to satisfy unmet needs; make reliability and service a habit, do what's right, not what's easy and impact the future through passionate global leadership. We offer a growing portfolio of more than 1,100 generic pharmaceuticals and several brand medications. In addition, we offer a wide range of antiretroviral therapies, upon which approximately one-third of HIV/AIDS patients in developing countries depend. We also operate one of the largest active pharmaceutical ingredient manufacturers and currently market products in approximately 150 countries and territories. Our workforce of more than 18,000 people is dedicated to improving the customer experience and increasing pharmaceutical access to consumers around the world.

## **About generic medicines in Australia**

Any generic medicine sold in Australia must meet the same strict standards of quality, safety and effectiveness applied to the original brand.

Before they can be sold, generic medicines are independently assessed by government, through the Therapeutic Goods Administration (TGA), to ensure that they contain the same active ingredient, in the same dose and deliver the active ingredient into the blood stream in the same way as the original brand. Also, while ever a generic medicine is available for sale, the manufacturer, doctors and pharmacists continue to monitor

the safety and effectiveness of the medicine, and report any significant issues to the TGA. By satisfying these criteria, the Australian public can be confident that a generic medicine will work in the same way as the branded medicine.

Generic medicines are a more affordable alternative for many patients. Every time a generic medicine is dispensed, it represents a significant saving to the nation. This adds to the long-term sustainability of the Pharmaceutical Benefits Scheme and provides for the funding of new, more expensive medicines needed to better manage diseases like cancer, diabetes and Alzheimer's disease.

### ***The Australian Context***

Australia is a small high-wage open economy contributing about 2% to the total OECD economy<sup>1</sup> and forming 1% of the global market for pharmaceuticals. From the viewpoint of maximising access to pharmaceuticals Australia would ideally seek to access medicines at their marginal cost of production, including of course a normal profit margin, but not a contribution to sunk research and development (R&D) overheads. Over the past four decades the brand pharmaceutical industry has systematically characterised this rational approach by smaller nations as 'free-riding' and has claimed that each country must contribute to the overhead costs of R&D.<sup>2</sup> Such a position would be more convincing if the brand pharmaceutical companies opened their books to government scrutiny and demonstrated that they have not yet achieved an adequate return to their risky investments from their primary markets. The reality is that R&D investments are already well recompensed by profits from the markets in which these global companies do most of their business. Further it is self-evident that the actions taken by small markets, such as Australia, will have no impact on the global production of pharmaceutical innovation. In 1984, Australia actively considered the option of not granting patents for pharmaceutical products.<sup>3</sup> This strategy of allowing patents for pharmaceutical processes but not for pharmaceutical products was the foundation of the strong leadership in chemicals and then pharmaceuticals taken by Germany.<sup>4</sup> It also underlay the strength and international competitiveness of Italy's (and subsequently India's) generic pharmaceutical industries. Had it followed such a path Australia might now have had a flourishing generics industry.<sup>5</sup>

The ideal outcome of negotiating prices that reflect marginal costs is constrained by the grant of patents, as this (a) allows the patentee to hold out for higher prices during the monopoly period; and (b) prevents generic supply should the patentee refuse to supply at the desired price. The patent system therefore operates as a major constraint on the ability to ensure access to medicines at the best (lowest) price.

Thus by signing up to TRIPS and TRIPS-Plus treaties, Australia has limited its capacity to maximise the goal of best-priced access to pharmaceutical products, except for products whose patents have expired. In considering the economics of patents and pharmaceuticals within the context of the PBS, it is therefore essential to consider separately the incidence and impact of evergreening pharmaceutical patents, the issues of on- and off-patent medicines, as well as the more complex case of treatments where alternative options are both off-and on-patent. There is also a need to consider separately the government's health goals and its

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<sup>1</sup> Using GDP as a measure of market size and 2009 data (the most recent year available) from the OECD ([http://stats.oecd.org/Index.aspx?datasetcode=SNA\\_TABLE1](http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE1) as at 4 August 2012).

<sup>2</sup> See, for example, the views of the CEO of Pfizer on introducing patent monopolies into the international free trade system ([http://www.iatp.org/files/Intellectual\\_Property\\_Rights\\_and\\_International.htm](http://www.iatp.org/files/Intellectual_Property_Rights_and_International.htm)). As Prof. Drahos has shown, Pfizer took the lead in promoting the TRIPS Agreement (See Peter Drahos (2002) *Information Feudalism: Who Owns the Knowledge Economy*, London: Earthscan).

<sup>3</sup> Industrial Property Advisory Committee (IPAC), 1984, *Patents, Innovation and Competition in Australia*.

<sup>4</sup> Graham Dutfield (2003), *Intellectual Property Rights and the Life Science Industries: A 20th Century History*, Burlington: Ashgate.

<sup>5</sup> Instead the global batten for the generic pharmaceutical industry passed from Italy to India. See Scherer, F.M. and Weisburst, S, 'Economic effects of strengthening pharmaceutical patent protection in Italy', *International Review of Industrial Property and Copyright Law*, 26(6), 1009-24.

industry policy goals. But in finalising any policy changes, changes in any one part of the system need to be assessed for their impact on other parts.

Before turning to these issues, it is important to consider the balance between market models and regulation in the very specific case of pharmaceuticals. There are three major forms of regulatory intervention into the pharmaceutical market. First, there are regulations to ensure that only products with an acceptable safety and efficacy profile are marketed; second there are regulations to restrain competition in respect of new pharmaceuticals (the patent system); and finally there is intervention to offset the effects of the patent system by providing subsidised access to medicines to ensure Australians can afford to access new patent-protected drugs. The intersection of these different regulatory interventions – each designed to achieve different policy outcomes – means that the pharmaceuticals market cannot be considered to work in the same way as other product markets.

### ***The Terms of Reference***

The Pharmaceutical Patents Review (PPR) is directed to “evaluate whether the system for pharmaceutical patents is *effectively* balancing the objectives of *securing timely access to competitively priced pharmaceuticals, fostering innovation and supporting employment in research and industry.*” The ‘system’, as the word is to be understood in the context of this submission, includes more than the ‘patent’ system. It includes all systems that are impacted by pharmaceutical patents and that are either directly or indirectly involved in meeting any of the stated objectives. The breadth of the PPR’s scope is reinforced by the need for the Inquiry to include an “assessment” of pharmaceutical patents on “competition, innovation and investment.” Accordingly, the system for the market authorisation of therapeutic goods administered by the Therapeutic Goods Administration (TGA), the system for the provision of subsidised pharmaceuticals under the Pharmaceutical Benefits Scheme (PBS) and the system for the implementation of the National Competition Policy as overseen by the Australian Competition and Consumer Commission (ACCC), are part of the “system for pharmaceutical patents”.

### ***Evergreening***

The word evergreening<sup>6</sup> should be understood to mean the extension of patent protection around a medicine or related medicine(s) beyond 25 years from the date the API is patent protected in Australia.

An evergreening patent does not necessarily create a complete barrier to competition. However, it may *significantly* impede or hinder competition at *any* point in time during the total period of patent protection. The word ‘significantly’ in this context means the patent is capable of preventing or has the potential to prevent, the production, sale or supply in Australia of a generic medicine identical to a listed, or previously listed, ARTG-brand medicine, in terms of either the process used for its manufacture or its composition, formulation, dosage, method of administration and its use in a method of treatment. There can be more than one evergreening patent. Typically evergreening patents will have overlapping periods of patent protection.

It is the density of evergreening patents around a medicine, regardless of whether they are challenged, that is also problematic for generic pharmaceutical companies.<sup>7</sup> Patents, even patent applications, may have a significant deterrent effect. A generic pharmaceutical company that is considering bringing a competing medicine onto the Australian market must first evaluate the patent landscape relevant to that medicine. Not

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<sup>6</sup> Chalmers, R., (2006), ‘Evergreen or deciduous? Australian trends in relation to the evergreening of patents’, *Melbourne University Law Review*, 30, 29-61; Faunce, T., Vines, T. and Gibbons, H. (2008), ‘New forms of evergreening in Australia: misleading advertising, enantiomers and data exclusivity: Apotex v Servier and Alphapharm v Lundbeck’, *Journal of Law and Medicine*, 16, 220-232; Vines, T. and Faunce, T. (2011), ‘Freedom of information applications as an “evergreening” tactic: Secretary, Department of Health and Ageing v INova Pharmaceuticals’, *Journal of Law and Medicine*, 19, 43-52.

<sup>7</sup> Pharmaceutical Sector Inquiry Final Report, European Commission (8 July 2009). One example mentioned in the Report involved 1,300 European patents around one medicine.

only is this mandated by the *Therapeutic Goods Act 1989*, but severe penalties, including criminal penalties,<sup>8</sup> apply to the responsible officers in regard to that evaluation in the context of an application to enter a generic version<sup>9</sup> of a brand medicine on the ARTG.

Complicating this process of assessment and evaluation is the opacity of the Australian Register of Patents. There is no capacity for anyone, expert or not, to search the Register and quickly, cheaply and readily identify all of the patents that pertain, relate or concern any medicine entered on the ARTG. It might even be suggested that some patentees deliberately go out of their way to camouflage patents using nondescript titles such as 'pharmaceutical compounds'<sup>10</sup> or 'extended release formulation'<sup>11</sup> without referencing them back to the either the relevant compound, API or medicine. The title 'pharmaceutical composition'<sup>12</sup> with or without the word 'novel' or other nondescript terms such as 'for external use' is another favourite. This situation is made many times worse when processes and intermediate products used in processes are taken into account.

The European Commission Competition Division's comprehensive investigation into the impact of medicinal patents on generic competition has provided important insights into the impact that evergreening patents have on the cost of healthcare. The period of the Competition Division's inquiry was 2000 to 2007 and covered all 27 member countries of the European Union. In its *Pharmaceutical Sector Inquiry Final Report*<sup>13</sup> the Commission concluded that healthcare expenditure would have been "about €15 billion higher without generic entry" and found first, that "originator companies apply patent strategies, which may interfere with the development of a competing medicine" and second, "any delay [to generic entry] will have a significant cost/ revenue impact [on the cost of healthcare]."<sup>14</sup>

## **Issues**

### ***The lack of a level playing field***

- While it is important to encourage investment in the research and development of new medicines, it is just as important to maintain an appropriate balance within the system so that the other half of the industry, namely the generics industry, is able to provide *timely access for Australians to quality, safe, efficacious and affordable medicines at a cost the PBS and taxpayers can afford*. There has been an overemphasis for far too long on meeting the needs and demands of one half of the pharmaceutical industry, namely, branded pharmaceuticals. Pharmaceutical patent owners now enjoy significant advantages over non-pharmaceutical patent owners in Australia.
- There is no level playing field in the pharmaceutical patent system in Australia.

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<sup>8</sup> s. 26B(2) *Therapeutic Goods Act 1989*.

<sup>9</sup> "generic product means a medicine that, in comparison to a registered medicine or a medicine that has been previously registered but is no longer a registered medicine (*previously registered medicine*): (a) has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the registered medicine or previously registered medicine; and (b) has the same pharmaceutical form; and is bioequivalent; and (c) has the same efficacy and efficacy properties." *Therapeutic Goods Act 1989*, Schedule 9, Part 1, subitem 1(1).

<sup>10</sup> AU 668159 (see Case Study 15). According to AusPat there are 99 unrelated patents using this title (as at 18 Jan 2013).

<sup>11</sup> AU 727653 (see Case Study 2). According to AusPat there are 99 patents using this title (as at 18 Jan 2013).

<sup>12</sup> According to AusPat there are 1946 unrelated patents using this term as part of the invention title (as at 18 Jan 2013).

<sup>13</sup> *Pharmaceutical Sector Inquiry Final Report*, European Commission (8 July 2009).

<sup>14</sup> *Ibid*, 521.

### ***Branded Pharma has not lived up to its promise of new medicines***

- In spite of the brand pharmaceutical industry having the benefit of the most harmonious patent laws since the turn of the 20th century there has never been a greater paucity of new drugs in the drug development pipeline as there is today.

### ***Policy disparity is the cause of systemic failure***

- Different policies, with different objectives, administered by different arms of government, is producing suboptimal outcomes for taxpayers. This disparity is the principal cause of a systemic failure in the pharmaceutical patent system.

### ***Evergreening is a consequence***

- The phenomenon called evergreening is one of the consequences of this systemic failure. Important medicines have been patent protected for periods of between 27 and 48 years. This has practically obliterated the 'spring-boarding' of generic medicines at the end of normal period of patent protection. And has unnecessarily added billions of dollars to the cost of the PBS.

### ***Recalibration must be a top priority***

- Thirty years ago the United States' Congress recognised the need to create balance in that country's health, innovation and competition systems. The Hatch-Waxman Act was the end result. Australia has not followed suit. Instead, Australia has imported selected features of Hatch-Waxman that only favour the branded pharmaceutical industry, e.g., patent certificates. This piecemeal approach has contributed to the imbalance of the system. Simply transposing fragments of Hatch-Waxman will not work. Australia has the PBS, while the United States does not. The United States provides significant incentives to generic companies to challenge patents, while Australia does not. If there is to be a viable and local generic pharmaceutical industry in Australia the recalibration of the system must be a top priority for Australia.

### ***Key findings of the Alphapharm study***

- Evergreening patents over incremental changes in medicines already available on the PBS delay generic entry thereby extending the period of time that the medicine remains in the PBS F1 formulary. This delays the application of a 16% price drop that would automatically occur on the market entry of a substitutable generic medicine. F1 medicines are also not subject to expanded and accelerated price disclosure.
- In the case of PLAVIX (clopidogrel) the cost to the PBS of a near 3-year delay in the generic market entry caused by the grant of an interim injunction over an evergreening patent that was subsequently revoked has been estimated to be about \$60 million. However, the total cost to the PBS attributable to the revoked patent has been estimated to be about \$644 million. Despite the fact that it was a term of the interim injunction that the patentee compensate any person adversely effected by the injunction, the Commonwealth and the generic companies involved have yet to be compensated. There is no statutory claw-back that empowers the Commonwealth to recoup the \$644 million it unnecessarily paid the patentee.
- In the case of EFEXOR (venlafaxine) and EFEXOR-XR (venlafaxine extended-release) the total cost to the PBS attributable to an evergreening patent over EFEXOR-XR that was subsequently revoked has been estimated to be about \$209 million. Had the evergreening patent not been revoked the PBS would have continued paying the much higher F1 formulary price for another 5 years, 4 months and 9 days. The validity of evergreening patents over PRISTIQ (desvenlafaxine) have not been challenged.
- PRISTIQ remains in the F1 formulary while EFEXOR and EFEXOR-XR are now in the F2 formulary. The difference in price is significant. The dispensed price of desvenlafaxine 100mg tablet medicine is currently \$50.52. This is a 14.3% price difference in favour of desvenlafaxine. This is particularly significant when it

is understood that there is no better health outcome. In the 2012-13 it is estimated that Wyeth will generate about \$90 million from PRISTIQ being on the PBS. These revenues vastly exceed the costs Wyeth incurred in applying for Australian patents, the costs of their continued upkeep and, importantly, the potential legal costs incurred in their defence (should one or more of the patents ever be challenged).

- Evergreening patents apply to medicines that are closely related to medicines that are already available on the PBS. These newer medicines may not necessarily produce better health outcomes than the older medicines but because they are treated differently by the PBS the newer medicines are placed in the F1 formulary. An example of this EFEXOR (venlafaxine) and PRISTIQ (desvenlafaxine). Typically doctors are encouraged through marketing to prescribe the newer medicine (more expensive) instead of the older medicine (less expensive). This typically occurs when the patent on the older medicine is about to expire. While it is still too early to provide full year data on the impact of generic competition since the relevant evergreening patent for EFEXOR-XR was invalidated mid-year in the 2011-2012 year, taking the latest available data into consideration, the cost of the prescribing shift to desvenlafaxine in that period is about \$8 million. Extrapolating forward to 2023 (when the last desvenlafaxine patent expires), that number grows to about \$257 million, assuming the prescribing shift to desvenlafaxine remains static at 2011-2012 levels.
- There is no improved health outcome of EFEXOR-XR over EFEXOR. There is no improved health outcome of PRISTIQ over EFEXOR.
- Another example is EPREX (epoetin alfa) and ARANESP (darbepoetin). In addition to the prescription shift to the newer more expensive medicine, the combined cost to the PBS of providing both the older and newer medicines significantly increases the total cost. Within two years of ARANESP being made available on the PBS the total cost of erythropoietin medicines went from about \$55 million to about \$76 million. By 2006 when the patent over EPREX expired the total cost had risen to about \$96 million. In other words, five years after ARANESP was approved by the TGA, the total cost of erythropoietin medicines had doubled. There is no improved health outcome of ARANESP over EPREX.
- Evergreening patents over the use of medicines for a new indication have been used to delay or prevent generic market entry even though a patent over the same medicine's use for an original indication has expired. Contributory infringement of the patents relating to the use in a new indication has been used as the basis for the grant of interim injunctions to prevent the generic market entry of the same medicine covered by an expired patent.
- At least 53 evergreening patents have been granted over LOSEC (omeprazole) and NEXIUM (esomeprazole) providing 48 years and 27 days patent protection. At least 29 patents have been granted over CIPRAMIL (citalopram) and LEXAPRO (escitalopram) providing 46 years, 7 months and 8 days patent protection. At least 48 patents have been granted over FOSAMAX (alendronate) providing 36 years, 5 months and 27 days patent protection. These are only three of 15 case studies. The case studies are not exhaustive.
- Evergreening patents include innovation patents which are virtually identical to subsequently granted standard patents over the same medicine.
- Evergreening patents include claims to methods of treatment. In the case of ZYPREXA (olanzapine) no less than 12 of the 22 evergreening patents concern methods of treatment such as for the treatment of cognitive dysfunction, depression, autism, excessive aggression, bipolar disorder, insomnia, pain, psychoses, substance abuse, migraine pain and refractory depression. The period of patent protection for olanzapine related medicines is 31 years, 3 months and 2 days.
- Evergreening patents include claims to combination of medicines even though the individual medicines are themselves no longer patent protected. An example is CADUET which combines atorvastatin (LIPTOR) with amlodipine (NORVAPINE). The result is that CADUET is in the F1 formulary while both LIPTOR and

NORVAPINE are both in the F2 formulary. The key patent over LIPITOR expired in May 2012. The evergreening patent over CADUET expires in 2020.

- Evergreening patents can also have their patent term extended. In the case of PLAVIX (clopidogrel) two evergreening patents had their respective patent terms extended. Both patents were challenged and subsequently revoked. The second of these extended the patent term by 5 years, from 2017 to 2022. The evergreening patent in question was over a medicine that combined clopidogrel with an antithrombotic agent. In the case of ZINNAT (cefuroxime) four out of the 21 evergreening patents had their patent terms extended, one by the full permissible 5-years. The total period of patent protection over cefuroxime medicines was 43 years, 7 months and 16 days. The last of the evergreening patents expired in 2007.

#### *Key problems with the current pharmaceutical patent system*

- The high economic costs to the PBS caused by the delay to generic market entry.
- A decision to enter the PBS market with a generic medicine is made only after a complex legal assessment of the many evergreening pharma patents.
- The lack of transparency of the Australian Register of Patents. This makes it very difficult for generic companies to undertake the complex legal analysis of patent protection. It is also very risky for the officials of generic companies that are required to sign patent certificates verifying that analysis in support of an application to the TGA for marketing approval of a generic medicine.
- Patent litigation is very risky and very expensive. The average cost is about \$4-5 million in legal costs alone. If the patent challenge is unsuccessful the legal costs rise to about \$7.5 million. There are also a considerable investment involved in preparing to bring a generic medicine to market. That investment must be financed. Typically, sales revenue is unavailable to assist in the financing of this investment as interim injunctions are granted very soon after market entry. If the patent challenge is unsuccessful that investment must be written off. The current reward to risk ratio before patent litigation will be approved is 10:1.
- It is the Commonwealth that ends up saving hundreds of millions of dollars when a pharmaceutical patent is successfully challenged as market entry moves the patent protected medicine from F1 to F2. Yet it is the generic companies that absorb the associated risks of patent litigation with no real incentive for doing so. First market mover is no longer a significant advantage given the impact of the 2007 and 2010 PBS pricing reforms, expanded and accelerated price disclosure for F2 formulary medicines and the intense level of discounting in the generic medicines market.
- Evergreening patents are not necessarily invalid. Indeed, under the very low patentability thresholds that currently apply (and will continue to apply for another 23 to 28 years) it is possible that they would be upheld by the courts as being valid. An example of this is LEXAPRO (escitalopram). The medicine contains a compound that is an enantiomer of citalopram. Contrast this to PLAVIX (clopidogrel) where the evergreening clopidogrel enantiomer patent was revoked.
- Low patent quality.
- The absence of any responsible independent agency (such as an IP Industry Regulator) tasked with ensuring that the standard of patent quality is high and having the power to intervene and mediate in a pharmaceutical patent dispute and, if necessary, to grant compulsory licenses or recommend the invoking of Crown use as a corrective or compensatory measure.
- The propensity of the Federal Court to restrain generic market entry.
- There is no requirement for pharmaceutical patentees to post cash bonds as a condition of the grant of an injunction.

- The undertaking as to damages is almost worthless as any party that wishes to be compensated under the terms of the undertaking must bring separate proceedings in the Federal Court. These proceedings are also very expensive, slow and technically and forensically complex requiring the claimant to prove market behaviour in support of their claim.
- The absence of any incentive system to encourage generic companies to mount challenges to evergreening pharma patents means that there will be fewer patent challenges in the future.
- The very limited capacity, or perhaps a complete reluctance on the part of the Australian government, to utilise its compulsory licensing and Crown use powers. Again, international trade agreements are relevant since they restrict the use of these powers.
- The absence of any effective financial or criminal penalties specifically designed to deter the abuse of the Australian pharma patent system. For example, at the present time there are no statutory provisions in the *Patents Act 1990* that facilitate the Australian government to recoup the cost to the Australian economy caused by an invalid patent (which by law is deemed to be void *ab initio*). There are also no general anti-avoidance provisions akin to those applicable to the Australian Taxation System. Accordingly, the gaming of the pharma patent system through evergreening is not expressly discouraged.
- The failure to thoroughly assess the claimed improved health outcome of 'new' medicine in terms of the grant of a patent and in its listing on the PBS.
- The inability for local generic manufacturers to produce patented medicines for export only markets.

### ***Alphapharm's proposed reforms***

#### ***A. Improving patent transparency and patent certificates***

1. Immediately require the entry onto the Register of Australian Patents (the Patents Register) the international non-proprietary name (INN), trade name and ARTG registration number, and if not available at the time then within seven days of ARTG registration, of any therapeutic good (as defined in s 3 Therapeutic Goods Act 1989) in respect to which a patent or patent application pertains, relates or is relevant to.
2. Immediately amend the *Patents Act 1990* so as to enable an ordinary person to freely, instantly, easily, accurately and electronically obtain from the Patents Register at any time:
  - a) An exhaustive list itemising each and every patent and patent application by reference to the international non-proprietary name (INN), the trade name or registration number of a therapeutic good (a pharmaceutical patent list);
  - b) a pharmaceutical patent list printed with a certified date and time stamp;
  - c) the identity and Australian address for service of the owner, including the beneficial owner, of a patent and patent application; and,
  - d) the identity and Australian address for service of any party that has an interest in a patent or any part thereof and including the following information:
    - i) the nature of such interest;
    - ii) the date and description of the document, if any, creating such interest;
    - iii) the commencing and ending dates of such interest;
    - iv) the geographical area encompassed by such interest; and

- v) if the interest is a licence to exploit the patent, the international non-proprietary name (INN), the trade name and ARTG registration number of the licensee's therapeutic good, and if not available at the time then within seven days of ARTG registration.
3. Immediately amend the *Therapeutic Goods Act 1989* so that a person providing a certificate pursuant to s. 26B(1) of the Act (a patent certificate) need not take into account any patent, or patent application, not included on a pharmaceutical patent list relating to a therapeutic good.
  4. Immediately amend the *Therapeutic Goods Act 1989* so that a person providing a patent certificate and relying on a pharmaceutical patent list in relation to a specific therapeutic good is not guilty of an offence under s.26B(2) of the Act; and,
  5. Immediately amend the *Patents Act 1990* so that it is not an infringement of a patent to market a therapeutic good if its international non-proprietary name (INN), trade or pharmaceutical name is not entered on the Patents Register.

***B. Improving patent quality, facilitating timely access for Australians to quality, safe, efficacious and affordable medicines at a cost the PBS and taxpayers can afford***

*Patentability standards*

1. Immediately amend, with retrospective effect, the *Patents Act 1990* so that a standard patent cannot be granted unless the specification discloses an invention that constitutes a *significant* advance over what was known and what was available to the public at the priority date of the patent.

*Limiting infringement of patents relating to therapeutic goods*

2. Immediately amend the *Patents Act 1990* so that a patent cannot be used to interfere, hinder or prevent the marketing of a therapeutic good if:
  - a) the authorised therapeutic good is not shown to provide a health outcome that is significantly better than that provided by another therapeutic good within the same therapeutic group; or
  - b) but for a use or methods of treatment claim in a patent the marketing of that good would not infringe that patent, unless the invention to which the claim relates is a significant advance over what was known and what was available to the public at the priority date of the patent.
3. Immediately amend the *Patents Act 1990* so that proceedings claiming infringement of a pharmaceutical patent must commence one year from the date on which the first infringing act occurred.

*Interim injunctions*

4. Immediately amend the *Patents Act 1990* so that a patent is not presumed to be valid by virtue of the act of grant.
5. Immediately amend the *Patents Act 1990* so that an interim injunction is unavailable as a remedy for patent infringement of a patent unless and until the patentee or, if applicable, the exclusive licensee, has posted a cash bond with the Federal Court, or other prescribed courts, of an amount equal to the value of the price reductions that would otherwise be applicable pursuant to Division 3A, *National Health Act 1953* during the period of time that the interim injunction would apply (the bond).
6. Immediately amend the *Patents Act 1990* so that if the bond has been posted and an interim injunction granted and the patent is ordered to be revoked, the bond becomes immediately payable to the Commonwealth on the entry of the revocation of the patent on the Patents Register.

### *Contributory infringement*

7. Immediately amend the *Patents Act 1990* so that the supply of a therapeutic good or a component thereof cannot constitute an act of contributory infringement unless there is an express indication to use that product in a manner that would infringe a patent.

### *Innovation patents*

8. Immediately amend the *Patents Act 1990*, with retrospective effect, so that an innovation patent cannot contain a claim relating, concerning or associated with a therapeutic good.

### *Challenging pharmaceutical patents*

9. Immediately amend the *Patents Act 1990* so that a remedy is available to any party that is the first to initiate revocation proceedings in the Federal Court, or another prescribed court, leading directly to the revocation of a patent or any claims, that would, but for that patent or its claims, prevent a therapeutic good being marketed in Australia (a pharmaceutical patent revocation award).
10. Immediately amend the *Patents Act 1990* so that a pharmaceutical patent revocation award, as damages, is an amount equal to the cost to the PBS attributable to that patent, compared with the cost to the PBS as if that patent had never been granted as determined by a legislated formula.
11. Immediately amend the *Patents Act 1990* so that on the payment of a pharmaceutical patent revocation award the recipient must pay one half of the amount so received to the Commonwealth within thirty days.

### *Patent term extensions*

12. Immediately amend the *Patents Act 1990* to clarify the meaning of 'pharmaceutical substance' so as to limit eligibility of patent term extension to the earliest patent to claim that substance in a pharmaceutical composition contained in a therapeutic good (the first pharmaceutical patent).

### *Ceased patents - clearing the patents register of superfluous patents*

13. Immediately amend the *Patents Act 1990* to revoke a patent that has ceased for a period of six months.

## **C. Promoting, monitoring and maintaining a pharmaceutical patent system that works to achieve a fair, balanced and equitable outcome for all Australians**

### *Pharmaceutical patent system oversight*

1. Establish the *Office of the Intellectual Property Regulator* being independent and given the responsibility to oversee the overall operation of the system and empower it to intervene and, when necessary, provide appropriate relief through mediation or due process of law.

### *Integrated policies*

2. Develop integrated policies that work to promote a strong and viable generic pharmaceuticals industry, while leaving intact a financial incentive for research and development of new medicines that provide significantly improved health outcomes.

### *Disincentives to abuse the system*

3. Amend the *Patents Act 1990*, the *Therapeutic Goods Act 1989*, the *National Health Act 1953* and the *Competition and Consumer Act 2010* so that each contains an objects clause that brings together a coordinated policy framework to create disincentives to behaviour that would unfairly and inappropriately exploit the system.

4. Amend each of these Acts so that, at a minimum, the Commonwealth is able to recoup the cost incurred by the PBS through the grant of a patent that is subsequently revoked.
5. Amend each of these Acts so that those responsible for unfairly and inappropriately exploiting the system are held responsible and accountable, both civilly and criminally, for the consequences of their actions.

*Manufacturing therapeutic goods for export*

6. Amend the *Patents Act 1990* so that Australian manufacturers of therapeutic goods may exploit the patent for the purposes of export if it would not *unreasonably* conflict with a normal exploitation of the patent and does not *unreasonably* prejudice the legitimate interests of the patent owner.

*Venlafaxine and Desvenlafaxine (EFEXOR, EFEXOR-XR and PRISTIQ)*  
*Indications: major depression, other anxiety disorders and panic disorder*  
Total cost to the PBS (2005-2012): \$765 million<sup>15</sup>

Venlafaxine is the API in a medicine first marketed in Australia under the trade mark EFEXOR. The base compound patent<sup>16</sup> over venlafaxine was filed in 1983 and granted in 1988. It expired in 2008 after 25 years. EFEXOR was first registered on the ARTG in 1994, about 11 months after the FDA approved EFFEXOR.<sup>17</sup>

The medicine marketed as EFEXOR-XR is simply an extended release version. The API is venlafaxine. There being two evergreening patents over EFEXOR-XR, the first was filed in 1997 and granted in 2001.<sup>18</sup> The second was filed in 2003 and granted in 2007.<sup>19</sup> Interestingly, while the second patent was revoked<sup>20</sup> in 2012,<sup>21</sup> the first remains active until 2017. EFEXOR-XR was first registered on the ARTG in 1998,<sup>22</sup> about seven months after the FDA approved EFFEXOR XR.<sup>23</sup>

Desvenlafaxine is the API in a medicine first marketed in Australia under the trade mark PRISTIQ. The evergreening compound patent<sup>24</sup> over desvenlafaxine was filed in 2002 and granted in 2008. It is active and expires in 2023 after a term of 21 years, 6 months and 7 days. A second evergreening method patent is also active.<sup>25</sup> It expires in 2022 after 20 years. PRISTIQ was first registered on the ARTG in 1998, about six months after the FDA.<sup>26</sup>

The venlafaxine and desvenlafaxine case study shows how the system allowed Wyeth (a subsidiary of Pfizer) to evergreen the base patent over venlafaxine so as to extend patent protection over EFEXOR using an extended release version of venlafaxine. The very low inventive step threshold, combined with no requirement to demonstrate a substantial improvement in health outcome over EFEXOR, enabled Wyeth to evergreen and thus hinder generic competition with EFEXOR-XR. It applied the same strategy to PRISTIQ (desvenlafaxine), which, again, has not been shown to provide any improved health outcome. The relevant evergreening patent over PRISTIQ expires in 2023. This patent has yet to be challenged.

<sup>15</sup> This figure includes EFEXOR, EFEXOR-XR and PRISTIQ.

<sup>16</sup> AU 567524.

<sup>17</sup> FDA Application No. (NDA) 020151 [EFFEXOR]. Approved 28 December 1993.

<sup>18</sup> AU 727653

<sup>19</sup> AU 2003259586. This patent is a divisional child of AU 727653.

<sup>20</sup> *Sigma Pharmaceuticals v Wyeth (No 3)* [2011] FCAFC.

<sup>21</sup> *Wyeth v Sigma Pharmaceuticals* [2012] HCATrans 116.

<sup>22</sup> TGA Approval Date: 11 May 1998.

<sup>23</sup> FDA Application No. (NDA) 020699 [EFFEXOR XR]. Approved 20 October 1997.

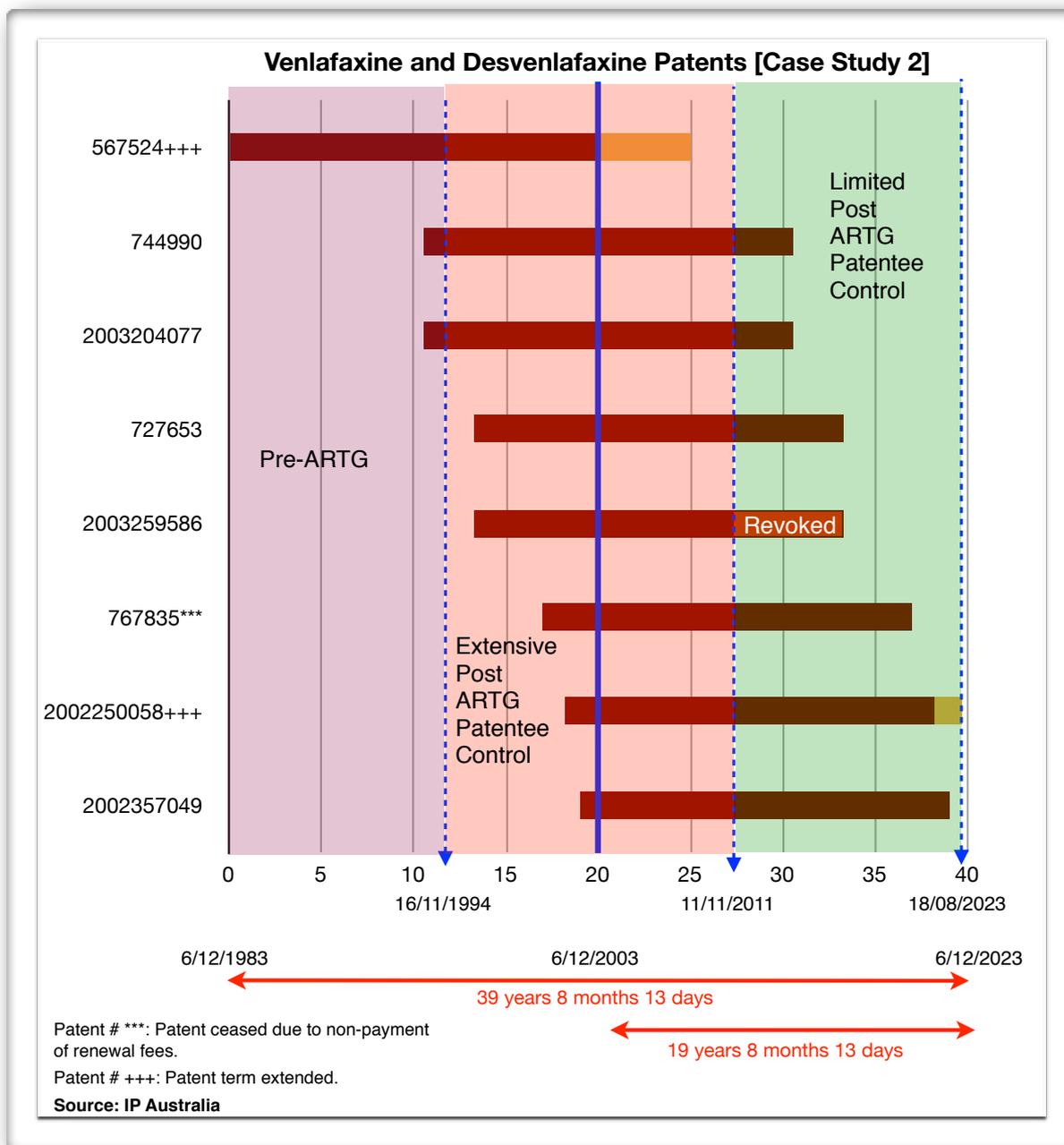
<sup>24</sup> AU 2002250058. This patent is a divisional parent of application AU 2007203410 which has lapsed.

<sup>25</sup> AU 2002357049.

<sup>26</sup> FDA Application No. (NDA) 021992 [PRISTIQ]. Approved 29 February 2008.

## Patent position

Through a series of evergreening patents, the expiry date for venlafaxine-related compounds and medicines has been significantly extended from 6 December 2008 to 18 August 2023, a period of 14 years, 8 months and 13 days. This is additional to the 25 years patent protection provided by the extended base compound patent. The result is that the total period of patent protection for venlafaxine-related compounds and medicines will reach 39 years, 8 months and 13 days unless these are successfully challenged and revoked.



Within this period Wyeth enjoyed marketing exclusivity over EFEXOR and EFEXOR XR for 16 years, 11 months and 27 days (from 16 November 1994 to 12 November 2011)<sup>27</sup>. And by the time the last evergreening patent expires in 2023<sup>28</sup>, it will have enjoyed marketing exclusivity over PRISTIQ for 15 years (from 18 August

<sup>27</sup> Alphapharm was enjoined from marketing venlafaxine-related medicines until 11 November 2011. It subsequently launched ENLAFAX-XR (Alphapharm) ARTG Entry 143552 Approval Date: 30 April 2009.

<sup>28</sup> AU 2002357049.

2008 until 18 August 2023).<sup>29</sup> Effectively, Wyeth will have enjoyed PBS market exclusivity over venlafaxine-related medicines for 28 years, 9 months and 2 days.

*The consequences of very low patentability standards - a subset of me too drugs*

Pharmacologically, venlafaxine and desvenlafaxine are closely related compounds. In fact, desvenlafaxine is the active metabolite of venlafaxine. Desvenlafaxine is formed by the liver even before venlafaxine reaches the systemic circulation, so that the clinical effect observed is produced by both venlafaxine and desvenlafaxine. Medically, they perform the same function. Scientific studies show that desvenlafaxine is no more efficacious than venlafaxine in the treatment of MDD.<sup>30</sup> The only apparent difference between them is the cost of treatment, especially since venlafaxine is now available as a generic medicine.<sup>31</sup>

In other words, Wyeth was able to extend the period of patent protection beyond the base compound patent because patentability standards are not only too low but they miss the point. The new, supposedly 'higher', patentability standards operating by virtue of the 'Raising the Bar' amendments will make very little difference in the context of the pharmaceutical industry. Instead, the same old legalistic and technical approach is adopted, albeit using slightly different language, with the result that, provided the 'invention' is not 'obvious' over the 'prior art', it will satisfy the inventive step threshold. However, the extent and scope of patent evergreening in the pharmaceutical sector is so widespread that the extremely large costs and serious inefficiencies the practice improperly imposes on the Australian economy demands a new approach. What is missing from the inventive step threshold is any qualitative assessment of the deliverable health outcome produced by a new medicine.

It is relevant to note that the European Medicines Agency (EMA), in accepting the withdrawal by Wyeth of its application for the EMA's approval of ELLEFORE, acknowledged two fundamental points. First, that "the effectiveness of [desvenlafaxine] had not been shown convincingly". Second, that "desvenlafaxine seemed to be less effective with no advantages in terms of safety and tolerability" compared to venlafaxine.<sup>32</sup> In its Withdrawal Assessment Report the EMA was pointed, describing the efficacy data supplied by Wyeth as being, "far from impressive."<sup>33</sup>

By contrast, the TGA not only agreed to place desvenlafaxine on the ARTG, but the PBAC made it available on the PBS on the basis that: "the data presented supported the claim of *non-inferiority* of desvenlafaxine to venlafaxine in the treatment of MDD and in terms of safety."<sup>34</sup> How then is 'non-inferiority' measured against the costs of treatment?

To be fair to the PBAC, at the time it considered the PRISTIQ application in July 2008, venlafaxine was still patent protected and therefore the price differential was not an immediate issue. Indeed, the patent challenge discussed earlier would not commence until 2009. However, the difference in PBAC's approach to that of the EMA (which was at the time facing precisely the same pricing issues as was the PBAC) is very relevant to this Review because it highlights what can occur when there are disparate and unconnected thresholds on a number of levels within the pharma patent system. Unless changes are made this will continue to have serious

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<sup>29</sup> EMEPAZOLE (Ranbaxy) ARTG Entry 184758 Approval Date: 9 February 2012.

<sup>30</sup> Sopko, M.A., Ehret, M.J. and Grgas, M. (2008) 'Desvenlafaxine: Another "Me Too" Drug?', *The Annals of Pharmacology*, 42, 1439-1446: "The main pharmacokinetic difference between desvenlafaxine and venlafaxine is their route of metabolism. Venlafaxine is metabolized primarily by CYP2D6 [Cytochrome P450 2D6, an enzyme], while desvenlafaxine is conjugated via UGT [Uridine 5'-diphospho-glucuronosyltransferase, an enzyme]" (at 1443).

<sup>31</sup> *Ibid*, 1445.

<sup>32</sup> EMA: Questions and answers on the withdrawal of the marketing application for Ellefore: 23 October 2008.

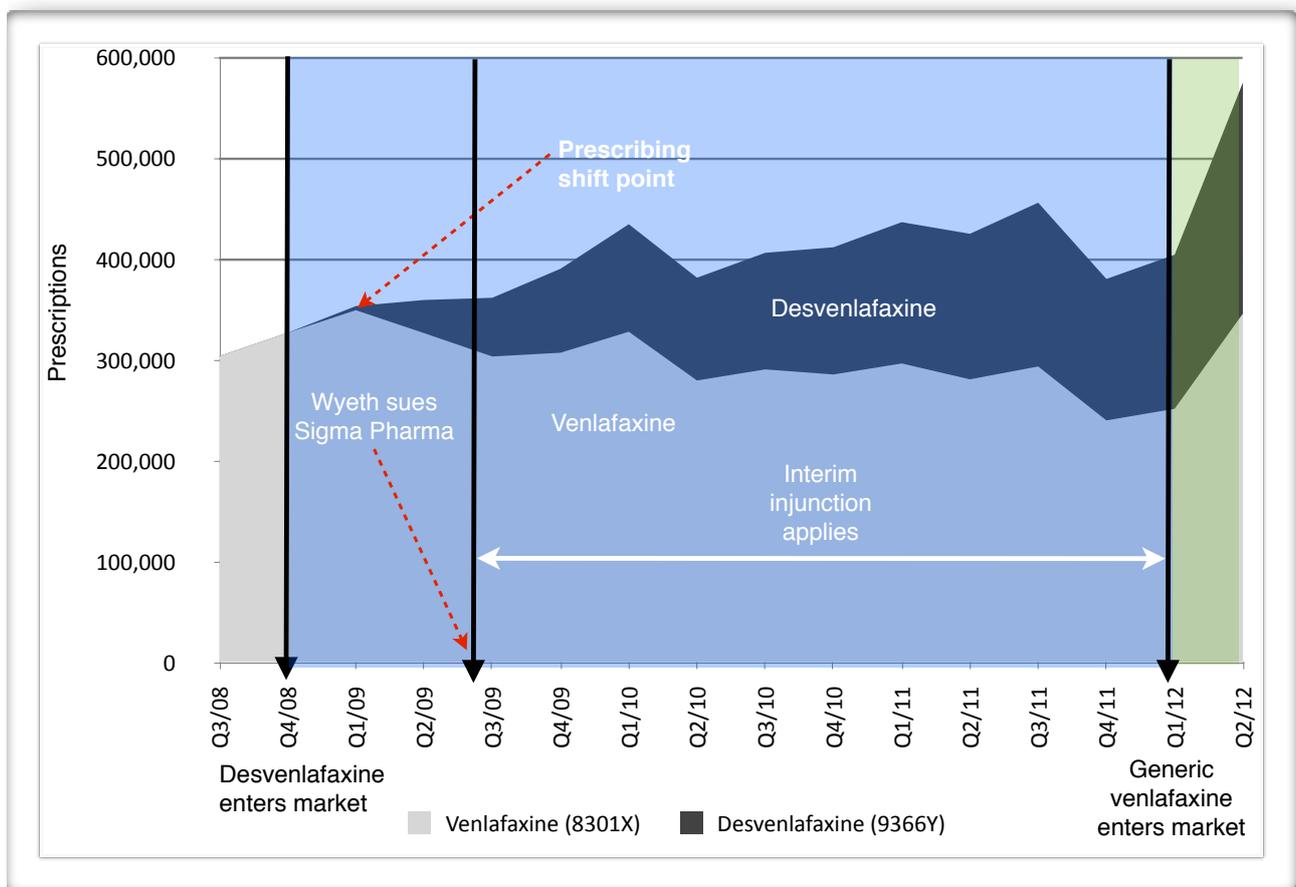
<sup>33</sup> EMA: Withdrawal Assessment Report for Ellefore: EMA/H/C/932: 22 January 2009.

<sup>34</sup> PBAC: Public Summary Document July 2008 PBAC Meeting: PRISTIQ: November 2008, 5.

ramifications for the overall cost of the PBS and the unnecessary diminution of the Commonwealth's consolidated revenues.

Moreover, there are some relevant observations that need to be made in the context of this example. These are as follows:

First, is the prescribing behaviour of medical practitioners which has significantly shifted towards desvenlafaxine. While this shift may not have been a significant cost issue in 2008, it is now as venlafaxine became subject to generic competition at the beginning of 2012. The dispensed price of venlafaxine (extended release) 150mg capsule medicines is currently \$44.20. The dispensed price of desvenlafaxine 100mg tablet medicine is currently \$50.52. This is a 14.3% price difference in favour of desvenlafaxine. The difference is directly attributable to 'evergreening' patents. These patents prevent generic competition and therefore keep desvenlafaxine in the F1 formulary. While it is still too early to provide full year data on the impact of generic competition since the relevant evergreening patent was invalidated mid-year in the 2011-2012 year, taking the latest available data into consideration, the cost of the prescribing shift to desvenlafaxine in that period is about \$8 million. Extrapolating forward to 2023, that number grows to about \$257 million, assuming the prescribing shift to desvenlafaxine remains static at 2011-2012 levels.



**Source:** [https://www.medicareaustralia.gov.au/statistics/pbs\\_item.shtml](https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml); quarterly data calculated.

Second, the price premium that favours F1 medicines is an encouragement to 'evergreen' pharma patents. Taking the Australian pharmaceutical market in isolation, the expectation - as conservative as it is - is that Wyeth will generate \$90 million from PRISTIQ being on the PBS. These revenues vastly exceed the costs Wyeth incurred in applying for Australian patents, the costs of their continued upkeep and, importantly, the potential legal costs incurred in their defence (should one or more of the patents ever be challenged).

*Relying on ad hoc patent challenges is not good policy if containing the cost of the PBS is a priority*

It must be appreciated that had one of the several evergreening patents<sup>35</sup> directed to certain aspects of the extended release version of venlafaxine-related medicines (EFEXOR-XR) not been successfully challenged<sup>36</sup>, the market exclusivity period for EFEXOR and EFEXOR-XR would have been increased from 16 years, 11 months and 27 days (from 16 November 1994 to 12 November 2011) to 22 years, 4 months, 5 days (from 16 November 1994 to 20 March 2017). Meaning that if this patent challenge had not taken place, EFEXOR and EFEXOR-XR medicines would have remained in the PBS's F1 formulary for another 5 years, 4 months and 9 days thereby preventing the Commonwealth from benefiting from the 16% price drop that came into effect after the interim injunction was lifted on 11 November 2011. Exacerbating the cost to the Commonwealth is the delayed introduction of the expanded and accelerated price disclosure (EAPD) system.<sup>37</sup> Indeed, had the only relevant patent been limited to the base compound patent<sup>38</sup>, venlafaxine would have moved from F1 to F2 on 6 December 2008, and not as happened, after the injunction was lifted on 11 November 2011.<sup>39</sup> And it is worth noting that if there had been no patent term extension, venlafaxine would have faced generic competition as early as 6 December 2003.

*Conclusion*

The high economic costs to the PBS caused by the delay to generic market entry reinforces the point made previously, that the Commonwealth's consolidated revenue is, in the context of the PBS, dependent on the actions of generic pharmaceutical companies. Ultimately, it is their decision to enter the PBS market with a generic medicine, made, as this example clearly shows, after undertaking a complex legal assessment of the many evergreening pharma patents and making a significant and very risky investment in bringing that product to market, that the Commonwealth ends up saving hundreds of millions of dollars. Part of the investment that generic companies make includes the cost of very expensive patent litigation.

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<sup>35</sup> AU 2003259586.

<sup>36</sup> *Sigma Pharmaceuticals v Wyeth (No 3)* [2011] FCAFC.

<sup>37</sup> The total cost to the Commonwealth is estimated to be about \$209 million.

<sup>38</sup> AU 567524 which expired on 6 December 2008.

<sup>39</sup> The total cost to the Commonwealth is estimated to be an additional \$50 million.

*Clopidogrel (PLAVIX)*  
*Indication: acute coronary syndrome*  
Total cost to the PBS (2005-2012): \$1.3 billion

Clopidogrel is the API in a medicine first marketed in Australia under the trade mark PLAVIX. The original patent<sup>40</sup> for clopidogrel was filed in 1983 and granted in 1986. It expired in 2003 after 20 years.<sup>41</sup> PLAVIX was first registered on the ARTG in 1998. As is typical, the FDA approval preceded TGA approval, in this case, by only 1 year and 16 days.<sup>42</sup>

#### *Patent position*

During the 20-year term of the original patent,<sup>43</sup> the patentee, Sanofi-Aventis (Sanofi), had the exclusive right in Australia to exploit clopidogrel, as a compound, to the exclusion of all others. Accordingly, anyone in Australia that exploited anything that came within the scope of the patent monopoly, such as using clopidogrel to make a different medicine to PLAVIX without the permission of the patentee, committed an act of patent infringement. In other words, a basic patent gives a patentee absolute control over the patented compound, in this case clopidogrel, and anything that could be done with it in Australia for 20 years. It is, of course, possible that a patentee may elect not to exploit its invention, nor permit any other party to exploit it. This is why patents are called negative rights since it is a right to prevent a third party from doing something rather than a positive right to allow something to occur.

Sanofi also applied for and was granted a series of evergreening patents designed to consolidate and extend the patent protection around clopidogrel. It obtained another 11 evergreening patents covering a range of so-called 'inventions' such as the processes used in the manufacture of the compound and medicine; variations to the compound clopidogrel, such as to a clopidogrel isomer<sup>44</sup> and a polymorphic form of clopidogrel<sup>45</sup>; formulations and combinational medicines containing clopidogrel and aspirin.<sup>46</sup> As a result, the total period of patent protection over clopidogrel came to 38 years, 7 months, 11 days.<sup>47</sup> Indeed, there is no absolute

The clopidogrel case study shows how imbalances in the system allowed Sanofi-Aventis to use the patent and legal systems to unjustifiably extend their period of exclusivity, thereby costing the Commonwealth over \$644 million if that were to occur today. Unfortunately, because it will not be financially viable for generic pharmaceutical companies to challenge evergreening patents, unless these imbalances are redressed, the generic pharmaceutical industry will no longer be able to fulfil its important checks and balances role in Australia.

<sup>40</sup> AU 554358.

<sup>41</sup> The patent term is calculated from the application date for the reason that, once granted, a patentee has the right to sue retrospectively for damages relating to any act of patent infringement that may have occurred from the date a patent application is open for public inspection (OPI date). However, these rights are unenforceable until the patent is sealed (s.61, Patents Act 1990). The sealing of the patent is the act that crystallises the patentees exclusive rights of exploitation.

<sup>42</sup> FDA Application No. (NDA) 020839. Approved 17 November 1997.

<sup>43</sup> 7 July 1983 to 7 July 2003.

<sup>44</sup> AU 597784.

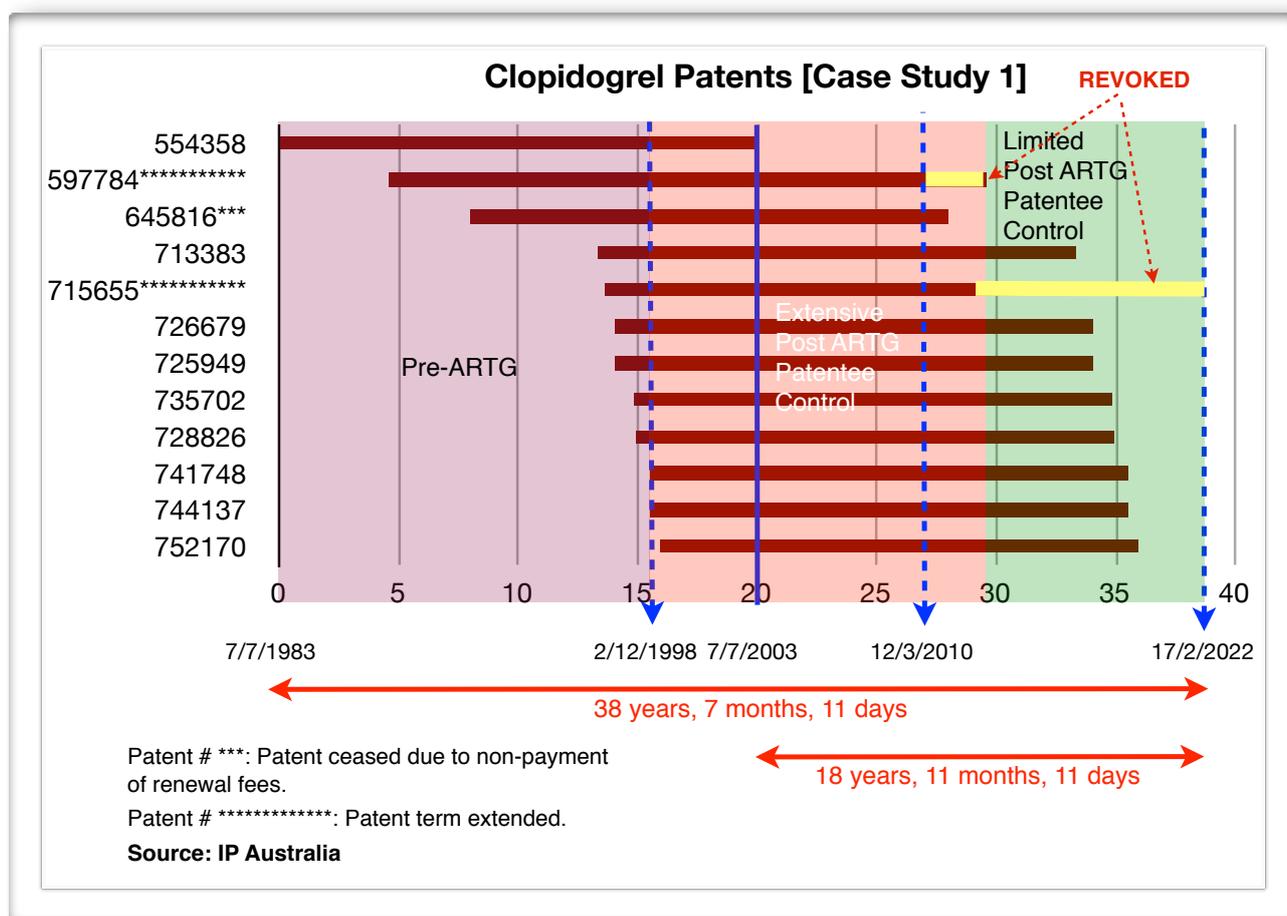
<sup>45</sup> AU 752170.

<sup>46</sup> AU 715655.

<sup>47</sup> 7 July 1983 (start date of AU 554358) to 17 February 2022 (expiry of AU 715655).

guarantee that this period may not be further extended by one or more subsequent evergreening patents. Sanofi has a further three pending patent applications.

Sanofi also filed a further 15 patent applications, which never proceeded to grant. While these applications did not result in a granted patent, they were nevertheless important to Sanofi's evergreening strategy because, even as pending applications, they had a deterrent effect to generic market entry in as much as their pending status created a significant legal uncertainty. Effectively, any proposed generic product launch necessitated an assessment as to the likelihood of grant and, if so, in what form. The assessment process itself was time consuming and expensive. And the outcome of such assessment led to a decision on how this might affect or block an upcoming generic product launch. This demonstrates that a patentee's ability to extract an economic rent from its patented invention is only one of a number of considerations relevant to the design of an evergreening strategy.



Sanofi was entitled to seek a patent term extension over clopidogrel. Crucially however, instead of basing its application on the original patent, it deliberately chose a later expiring evergreening patent.<sup>48</sup> The reason for this choice is obvious. It wanted to maximise PBS revenues. The longer it could push out the period of exclusive patent protection, the longer clopidogrel would remain in the F1 formulary and the greater the PBS revenues. Sanofi realised that by extending the patent term of the evergreening patent, the exclusivity period was pushed out from 7 July 2008 (the expiry date of the original patent) to 4 February 2013 (the expiry date of the extended evergreening patent).

<sup>48</sup> AU 597784.

### *Cost to the Commonwealth*

Subsequent patent litigation<sup>49</sup> held the evergreening patent invalid *ab initio*. The evergreening patent was eventually revoked on 12 March 2010, about three years before the expiry of the extended term. The consequential saving to the Commonwealth, based solely on the automatic price reduction applicable to F2 medicines, has been estimated to be about \$60 million. This sum does not take into account the benefits of further price reductions that would have applied with the price disclosure process. Nor, the amount that the Commonwealth overpaid the patentee while PLAVIX remained in the F1 formulary from the time the original compound patent expired on 7 July 2003. The effect of the evergreening patent was to delay generic competition by nearly seven years. If this were to occur today under the currently applicable legislation, the cost to the Commonwealth would be about \$644 million.

The problem for the Commonwealth is that while it may seek to recover the \$60 million under the terms of the interim injunction, it has no statutory claim to recover the overpayment that the patentee receives under the system. And the Commonwealth's inability to statutorily claw-back this overpayment, which in the case of clopidogrel could have been in the hundreds of millions of dollars, creates an enormous inducement to game the pharmaceutical patent system, in addition to leaving an enormous hole in the Commonwealth's consolidated revenue.

This result makes little sense from a policy perspective. It is akin to the Australian Tax Office (ATO) being unable to recover the underpayment of income tax from a taxpayer that makes a claim for a tax deductible item that is subsequently disallowed. Clearly, this would, if it were the case, negatively impact on the Commonwealth's consolidated revenue. Moreover, it would do nothing to modify inappropriate and illegal taxpayer behaviour. The underpayment of income tax to the ATO and the overpayment for a pharmaceutical by the PBS has the very same effect on the Commonwealth's consolidated revenue, namely, its diminution. Imagine the state of the Commonwealth's finances if a similar approach were adopted by the ATO in regard to income tax collections, or by Centrelink in regard to welfare payments.

### *Extended marketing exclusivity based on an invalid patent*

The evergreening patent in question<sup>50</sup> was an 'enantiomer' patent. To understand what an enantiomer is one needs to know that the clopidogrel molecule contains a carbon atom bonded to four different groups. This is called a 'chiral centre' and its effect is that clopidogrel has two possible forms, called stereoisomers or more specifically enantiomers. These two enantiomers are mirror images of each other, in exactly the same way as one's left and right hands are mirror images of each other. *Racemic* clopidogrel is a mixture containing equal quantities of both enantiomers. The S-enantiomer can be identified because it rotates plane polarised light in a positive direction. In contrast, the R-enantiomer rotates plane polarised light in a negative direction. The presence of 'chiral centres', enantiomers and racemic mixtures have been long understood.<sup>51</sup> It has also been long understood that enantiomers behave differently biologically and that one enantiomer will usually be more pharmaceutically efficacious than the other, often with one enantiomer having all of the activity and the other enantiomer being inactive.

This patent, on which Sanofi obtained an extension of term, claimed as an invention one of the two known enantiomers of clopidogrel, the S-enantiomer (also known as the dextro-rotary enantiomer or the (+) enantiomer).

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<sup>49</sup> *Gen-Rx v Sanofi-Aventis* [2007] FCA 1485; *Apotex (formerly Gen-Rx) v Sanofi-Aventis* [2008] FCA 1194; *Apotex v Sanofi-Aventis* [2009] FCAFC 134; *Apotex v Sanofi-Aventis* [2012] HCATrans 357.

<sup>50</sup> AU 597784.

<sup>51</sup> Enantiomers were first discovered by Louis Pasteur in 1848.

One of the alleged grounds of invalidity was that the original patent disclosed the S-enantiomer. As is apparent, the subject of this evergreening patent was not for a new compound. The minimum level of invention required, even under the then applicable patent thresholds, was not satisfied.<sup>52</sup>

#### *Use of the legal system to maximise exclusivity*

Nevertheless, in 2007, some four years after the original compound patent had expired, the patentee relied on this evergreening patent to sue two generic pharmaceutical companies for patent infringement. The litigation trigger was a patent certificate provided by Apotex and Spirit Pharmaceuticals under s.26B(1), *Therapeutic Goods Act 1989*. In its certificate, Apotex declared that the generic version of PLAVIX “would not infringe a valid claim” of the evergreening patent. The provision of a patent certificate is mandatory and it is a criminal offence to make a false statement in relation to its contents. Apparently, Apotex, after undertaking a thorough assessment of the legality of the evergreening patent had come to the conclusion that it was invalid.

On the basis of the broad patent that was granted, Sanofi sought an interim injunction to prevent the marketing of the generic versions of PLAVIX. This was critical to its objective, which was to extend the period of marketing exclusivity to the maximum possible. In order to do so, and thereby delaying the movement of PLAVIX from the F1 to the F2 formulary to prevent triggering an automatic 12.5% price decrease to the PBS price, Apotex and Spirit had to be restrained from launching their respective products on the Australian market. The injunction was granted by the Federal Court on 21 September 2007. The judge was persuaded “by the effects of disturbing the status quo, particularly as it relates to the operation of the PBS.” His reference to the PBS was to the “irreversible” price decrease applicable to PLAVIX when it moved into the F2 formulary.<sup>53</sup> Moreover, it quarantined PLAVIX from the process of price disclosure and any further price reductions applicable to all F2 medicines.

As is the convention, the Court required the patentee to proffer an undertaking as to damages. Under the terms of that undertaking it agreed to:

- (a) submit to such order (if any) as the Court may consider to be just for the payment of compensation, to be assessed by the Court or as it may direct, to any person whether or not a party, adversely affected by the operation of Order 1 set out below or any continuation (with or without variation), and,
- (b) pay the compensation referred to in (a) to the person or persons there referred to.

In the meantime, while the litigation on the merits continued on to a first hearing before a single judge of the Federal Court,<sup>54</sup> followed by an appeal to the Full Federal Court<sup>55</sup> and, finally, by an application for special leave to appeal to the High Court,<sup>56</sup> a process that took a further 2 years and 9 months, the PBS continued to pay the higher than normal F1 price for PLAVIX.

#### *Litigation imbalance and risk to the Commonwealth revenues.*

The legal costs associated with patent litigation, which is inherently technical and complex, are very high and usually exceed \$5 million per patent. Contributing to the cost of patent litigation is executive time loss. And the high risk of losing is also significant, as the losing party bears the additional burden of paying a significant

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<sup>52</sup> s.18(1) *Patents Act 1990*.

<sup>53</sup> *GenRx v Sanofi-Aventis* [2007] FCA 1485, para 15.

<sup>54</sup> *Apotex v Sanofi-Aventis* [2008] FCA 1194.

<sup>55</sup> *Apotex v Sanofi-Aventis* [2008] FCAFC 134.

<sup>56</sup> An application for special leave to appeal was heard and refused by the High Court on 12 March 2010.

proportion of the winning side's legal costs. Beyond the litigation costs are the regulatory, production and marketing costs that are incurred in the lead up to the market launch of a generic pharmaceutical. These costs are substantial and, should an interim injunction be granted, need to be financed for about three years without any incoming sales revenue during this time to offset the financing costs. This can result in manufacturing product going past its sell by date and having to be destroyed.

Most importantly though, a generic pharmaceutical company must also weigh up the potential financial claims it will face from the patentee in the form of damages if the patent is subsequently found to be patentable and infringed. For example, upon the entry of a generic medicine into the pharmaceutical market, the brand medicine moves from the F1 to the F2 formulary. This movement triggers a 16% price drop on the brand medicine. As a result, and in the event that the challenged patent is upheld as valid, the generic pharmaceutical company that is responsible may face a significant damages claim.

The generic pharmaceutical company must, therefore, weigh up on the one hand the potential profit made from a generic launch against all of the negative factors listed above. As can be seen, the potential downsides currently far outweigh the potential upsides. Consequently, a generic pharmaceutical company will only decide to challenge a potential invalid pharmaceutical patent after coming to a commercial decision based on its assessment of the risks associated with bringing a patent challenge.

In marked contrast, the patentee faces a very different risk profile. By initiating litigation, it defends its revenue stream for several additional years at very little relative cost compared against the high revenues it is generating through continued exclusivity. If it ultimately loses, currently, the damages that it will face will be a fraction of the total revenue it has unjustifiably obtained. Therefore, from a patentee perspective, the decision to litigate is usually straightforward.

As a result, most pharmaceutical patents remain unchallenged not because they are necessarily valid but because the reward to risk ratio in challenging them is far too low. Effectively, the Commonwealth's consolidated revenue, in so far as the PBS is concerned, is positively impacted by a successful patent challenge brought by generic pharmaceutical companies. However, as a result of the already discussed 2007 PBS Price Reforms and other recent market-related behaviour, such as has occurred with LIPITOR,<sup>57</sup> the growing disequilibrium within the pharmaceutical patent system means that generic pharmaceutical companies are experiencing rapidly and significantly diminishing revenues while facing the same high risks, expense and delay that typifies patent litigation. At the same time brand pharmaceutical companies continue to enjoy very high returns while their medicines remain price protected in the F1 formulary and face little risk should any of the many evergreening patents around an F1 medicine be revoked. Indeed at the present time, even if such a patent is revoked brand pharmaceutical companies retain the PBS revenues earned before revocation. This effectively provides them with a significant windfall that comes at the expense of the PBS. As already discussed, this makes little sense from a policy perspective. Not only does it negatively impact on the Commonwealth's consolidated revenue, but also it provides a huge incentive to evergreen. There is virtually no downside that a brand pharmaceutical company faces, other than the movement from F1 to F2 and the subsequent automatic price drop that accompanies it. In effect, the pharmaceutical patent system rewards evergreeners.

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<sup>57</sup> Harvey, K (2012) 'Companies tussle over market share for anti-cholesterol drug Lipitor and its generic equal, *The Conversation*, 18 May 2012.

A consequence of this ever increasing imbalance is that there will be fewer patent challenges in the future with the result that the cost of medicine to the Commonwealth will be much higher than it otherwise might need to be. Unless this imbalance is redressed, even raising patentability thresholds will not be enough to encourage the generic pharmaceutical industry to challenge evergreening patents and if the generic industry is no longer able to perform this crucial 'checks and balances' role then the cost of medicine to the PBS will increase.

#### *Strategy repeated with a 'use' patent*

Applying for an extension of term based on an invalid evergreening patent was not the only way that Sanofi was able to 'game' the system to its advantage. It also used a combination patent<sup>58</sup>, which was also ultimately held to be invalid, to obtain yet further commercial advantage at the cost of the Commonwealth. The combination patent had a maximum expiry date of 17 February 2022 having been granted a five-year patent term extension providing the patentee with 25 years patent protection. Claim 1 of the patent defined the invention as follows:

Pharmaceutical composition containing clopidogrel and aspirin as active ingredients, in which the active ingredients are present in the free state or in the form of a pharmaceutically acceptable salt.

The invention is directed to the mere combining of two well known compounds with well known efficacies into a single medicine. It is unfortunate that IP Australia would grant such a patent in the first place and patentability standards should be of a level that this sort of patent is not granted. It is furthermore highly undesirable that this patent is eligible for an extension of term, given that the basic compound, clopidogrel, had already received a five-year extension of term on the subsequently revoked enantiomer patent.

Clopidogrel is marketed as a mono product with two indications: the use of clopidogrel on its own in the treatment of vascular ischaemia associated with atherothrombotic events; and the use of clopidogrel in combination with aspirin in the treatment of acute coronary syndrome.

Apotex initiated a revocation action to remove the combination patent on clopidogrel and aspirin<sup>59</sup> but Sanofi-Aventis resisted up to the first direction hearing on 29 May 2012 when it suddenly chose not to defend the patent and consented to its revocation. This action was a clear concession of invalidity, suggesting that Sanofi readily accepted the weakness of the relevant patent, yet it chose to initially contest the challenge and prolonged the life of an invalid patent, thereby unfairly and inappropriately delaying generic competition.

The effect of this patent on generic competition has been significant. Its presence has meant, despite the revocation of the enantiomer patent in 2008 and the subsequent launch of generic clopidogrel medicines in 2010, that none of the generic clopidogrel medicines include the acute coronary syndrome indication.

The patent has also had a significant effect on generic launches of combination products containing clopidogrel sold by the patentee, namely COPLAVIX, DUO PLAVIX and DUOCOVER<sup>60</sup>, all containing combinations of clopidogrel and aspirin. Despite the revocation of the enantiomer patent in 2008, the first launch of a combination product did not occur until late 2012. This was solely due to the continuing presence of the invalid combination patent and this caused an additional loss to the Commonwealth.<sup>61</sup>

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<sup>58</sup> AU 715655.

<sup>59</sup> AU 715655.

<sup>60</sup> This is licensed to Bristol-Myers Squibb Australia Pty Ltd.

<sup>61</sup> This figure is estimated to be about 11 million.

### *Conclusion*

In summary, clopidogrel is a good example of how brand pharmaceutical companies, in this case Sanofi, are able to inappropriately exploit a system that permits evergreening patents and then use them to delay generic competition for many years. In the case of clopidogrel, this resulted in an unjustified period of exclusivity after 7 July 2003 and came at a huge cost the Commonwealth.