Attachment C: Pharmaceuticals: an insight into patent standards and costs

This as-yet unpublished paper is provided here, as an attachment to my submission, ***Empirical evidence on patents and data protection: Response to the Productivity Commission's Issues Paper on Intellectual Property Arrangements****.*

It provides details on the costs to taxpayers of uninventive secondary pharmaceutical patents.

Hazel V J Moir*

Abstract: Litigated pharmaceutical patents are a valuable source of data on both how the patent system actually operates and where savings might be made in pharmaceutical outlays. Although innovation is central to economic growth and the competitiveness of firms, little is known of its costs nor of the quantum of inventiveness required for a patent. Two cases of litigated pharmaceutical patents demonstrate that very little inventiveness is needed to obtain a patent and that the consequence is much higher PBS outlays. There are clear policy implications.

* The views presented in this paper are my own and do not represent the views of any other person or organisation. I would like to thank Professor Luigi Palombi for input in identifying and interpreting both patents and legal judgements.

Pharmaceuticals: an insight into patent standards and costs

1. Setting the scene

Charging very high prices for life-saving drugs is not an abuse of the patent system. It is exactly the kind of outcome patents are designed to achieve – new products induced by the reward of a monopoly period. However when strategies are employed to undermine the social objectives of the patent system by extending monopolistic control in time or scope, this is an abuse. Machlup identified "successive patenting of strategic improvements of the invention which make the unimproved invention commercially unusable after expiration of the original patent" and "creation of a monopolistic market position based on the goodwill of a trademark associated with the patented product or process, where the mark and the consumer loyalty continue after expiration of the patent" as two of a very small list of patent abuses (Machlup, 1958: 10-11). Pharmaceutical “lifestyle management” uses these two strategies – successive patenting of improvements (“evergreening”) and trademarks to build consumer and prescriber loyalty.

In countries with social programs to ensure drugs are affordable, data on government outlays on pharmaceuticals can be used to estimate the cost of these strategies. Volume data allow tracking of brand switching between older off-patent medicines and newer on-patent substitutes, and price data allow estimates of the cost. Patent data, particularly where there has been litigation, provide clear insights into the nature of the “improvements” in evergreening patents. The rules which allow additional patents for small improvements can also be identified, and the cost of these rules estimated. Pharmaceutical evergreening thus provides a rare insight into the financial cost of low patent standards.

It is generally assumed that patents are only granted for genuine inventions. This is far from the truth (Moir, 2013). The data presented here both confirm the negligible quantum of inventiveness required for patent grant and provide estimates of the cost of granting such very low standard patents. This material is useful empirical input to the current Productivity Commission (PC) Inquiry into Intellectual Property Arrangements and to current considerations of the proposed Trans Pacific Partnership Agreement (TPPA).

1.1 Patents and evergreening

Where large lumpy investments are combined with a relatively fast ability to imitate an invention, the market for invention may fail and useful new inventions will not attract the requisite investment. This perspective on the rationale for patents particularly characterises the pharmaceutical industry.

Efficient and effective patent policy is that which most closely approximates to two conditions:

(i) patents are granted only for inventions which would not otherwise occur; and

(ii) patents are granted only where the social benefits (private plus spillover benefits) exceed the social cost of the monopoly grant.

Although there are differing views on the cost of Phase III clinical trials,[1] where these are high and the outcome is a new active pharmaceutical ingredient (API) offering a real improvement in health outcomes over existing and related drugs, the invention meets both conditions and the grant of a patent is relatively non-controversial. However, where the invention is a modification of the original API, the argument in support of patent grant is considerably weakened. The impediment to the invention can be low and social benefits can be small or non-existent. An efficient patent system ought to reject such applications.

Low-quality patents surrounding an original patented invention are generally referred to as secondary patents. Those owned by the owner of an original API patent are known as evergreening patents. Even very weak (uninventive) patents are valuable to originator companies as the returns from extra exclusive time in the market will "easily outweigh the costs of patent litigation" (Burdon and Sloper, 2003: 238).

Whether evergreening patents involve sufficient benefit to society to merit a patent is a matter for empirical assessment. Because there is limited appreciation of just how low the patent inventiveness requirement is, this detailed analysis of two types of pharmaceutical patent adds new understanding of how the patent system works in practice. Given the centrality of invention and technological change to economic growth, and understanding of how the patent system does (or does not) work is also important to innovation policy.

1.2 Using trademarks to establish brand loyalty

An integral part of evergreening strategy is using trademarks to establish both consumer and prescriber loyalty. Originator companies are highly effective in persuading medical practitioners to prescribe new versions of old drugs. The high share of revenue spent on marketing by originator pharmaceutical companies is well known – the average spend on marketing and promotion is 23 per cent of turnover compared to 17 per cent on R&D (European Commission, 2009: 7-8).

TRIPS Article 15 defines trademarks as signs "capable of distinguishing the goods or services of one undertaking from those of other undertakings" – that is the focus of the trademark is on **company** identity, not on brand or product. This aligns with the original purpose of trademarks – to ensure consumers could select their desired price/quality range and that both consumers and producers can take action in case of counterfeit products.

The current WTO dispute over plain packaging of tobacco products is of considerable relevance to the issue of using trademarks for specific drugs, rather than simply company names. In both cases companies use multiple brands to extend consumer loyalty over time. The potential confusion caused by multiple trademarks for the same medicine can be used to persuade courts to grant injunctions over generic entry.

2. Existing knowledge and methodology

A small empirical literature on evergreening patents has emerged, largely in respect of the USA.[2] Additional low quality patents are commonly taken out late in the life of higher sales drugs adding, on average, 6.5 years to patent life (Kapczynski et al., 2012). The average number of patents per drug has increased over time, with more patents per drug where

[1] See Light and Warburton (2011) for a critique of industry estimates of clinical trial costs.
[2] For a more detailed review of the evergreening literature, see Moir et al., 2014.

there was priority Federal Drugs Administration approval or a term extension. These two variables are associated with "block-buster" medicines, where there are over 5 patents/drug in the 2002-04 period (Ouellette, 2010: 316). Hemphill and Sambat (2012) find an average of 2.7 patents per API, with a median of two. The strongest predictors of patent challenges are a longer patent term and the presence of evergreening patents (themselves correlated), suggesting that patent challenges are a response to evergreening. Adding to these macro-level studies, Amin and Kesselheim (2012) investigate evergreening patents over two HIV drugs, both owned by Abbott (ritonavir and lopinavir). They identified 82 granted patents and 26 applications covering compositions/formulations, processes, treatment methods and/or general patents.

In Canada the number of patents per drug is much higher at a mean of 40 (Bouchard et al., 2010). The one Australian study on secondary (rather than evergreening) patents finds an average of 49 patents per API for the 15 drugs with the highest outlays in 1990-2000 (Christie et al., 2013). About 25 per cent of these are held by the originator company, giving an estimate of around 12 evergreening patents/drug.

The much lower average number of evergreening patents found in the USA than in Australia or Canada can partly be attributed to the strong US incentives provided for generic challenge of weak patents. A company challenging a patent bears all the risks and uncertainty but shares the reward (market entry) with all other competitors, creating a very low incentive to challenge even a very weak-seeming patent. The US reward is a 180 day period of market exclusivity for a challenge which results in first generic market entry (Holovac, 2004). Given the size of the US medicines market, this is a substantial prize, easily outweighing the cost and risks of litigation.

2.1 Selecting cases for study

Identifying all the patents relating to a single pharmaceutical compound (API) is not a simple matter. Searches of official patent databases can be incomplete, and need to be augmented by searches using commercial databases and/or professional searchers. The initial intention was to investigate a set of drugs identified on the basis of total Australian outlays in a given year. However, a set of 15 cases where the evergreening patent search had been completed by an experienced patent attorney showed much more complete results. A cross-check of the five cases common to both datasets demonstrated that only the latter reliably identified all evergreening patents (Moir and Palombi, 2013).

This created a difficult choice between representativeness and reliability. The advantage of a case study approach is the depth of information it provides on evergreening patents. A small number of cases can never be fully representative, but they can reliably demonstrate the kinds of issues raised by evergreening. But in-depth material can become overly complex. To avoid this two cases were selected here, each involving similar issues. Both demonstrate the patenting of variant chemical formulae together with patenting combinations of known compounds and known drug delivery mechanisms (e.g. immediate, delayed, extended release). The focus on these two cases allows a clear identification of just how little inventiveness is required for grant of a pharmaceutical patent.

Data used in the analysis include bibliographic information for each patent, content from the patent specifications and court decisions (where there has been litigation). In some cases data and analysis are available from secondary sources. A particular focus of each case is identifying the economic impact. Data on the number of Pharmaceutical Benefits Scheme

(PBS) prescriptions, combined with price data, allow relatively robust estimates of the cost of patenting than is usual.

Under Australia's PBS, consumers pay a fixed maximum price and the difference between this and the agreed dispensed price is paid for by the government (taxpayer). The bulk of medicines prescribed in Australia are those listed on the PBS, and originator pharmaceutical companies certainly see PBS listing as essential in gaining a good return from the Australian market. Once a generic product enters the market the PBS price falls, initially by a statutory 16 per cent. The price then falls further following reported actual prices, but with a 12 to 18 month delay. The cost of delaying generic market entry can thus be estimated, providing an approximate minimum estimate of consumer losses. There are no data to estimate the loss to generic companies from delayed entry.

An important variable in the analysis is the effective monopoly period. Most patented products undergo a development and commercialisation process during the early years after patent filing. In all technology fields there is a delay – often substantial – between patent filing and entry of a product into the market. Pharmaceutical companies have successfully argued that these delays are particularly severe in the medicines industry due to regulations designed to protect the public from unsafe or ineffective drugs. On this basis they have, through TRIPS, gained a global extension in patent term to 20 years for all technologies. Through bi-lateral trade treaties, the pharmaceutical industry has also gained possible five year patent term extensions (PTE) if the regulatory approval process has been long.[3]

The ***effective monopoly period*** is defined as the period between the date the drug is approved and the expiry date of the relevant patent. This period is much shorter than 25 or even 20 years. Hemphill and Sambat (2012: 330) measured the effective monopoly period in the USA using the approval date of the first generic product. For the 119 drugs in their sample they found this ranged from 5.8 to 19.0 years with a mean of 12.15. In Australia the maximum effective monopoly period is 15 years, and 53% of pharmaceutical patents with PTEs achieve this (Harris et al., 2013: 60).

3. The case studies

The two cases presented here are among the 50 most expensive drugs on the PBS. Their key features are shown in Table 1. Both have involved litigation, with quite different outcomes, and the additional material from these judgements provides useful insights into the quantum of inventiveness involved. One case involves only eight evergreening patents while the other has 61. But while the volume of evergreening patents can increase sorting and analysis costs for generic companies, it is the *character* of the patent that is more important in determining its ability to successfully block generic entrants. In each case there were two key evergreening patents that delayed generic entry.

Each case involves the patenting of a chemical compound closely related to that for which an initial patent was granted. This variant compound subsequent enters the market as a separately trademarked "new" medicine. Volume data for PBS medicines from 1993 allow

[3] Introduced in 1998, this provision was written into the Australia United States Free Trade Agreement (AUSFTA), thus making it virtually impossible to change. This is unfortunate as the Pharmaceutical Patent Review found no evidence that patent term extensions were "contributing to the development of the Australian industry or to Australian R&D in a way that is commensurate with its very substantial costs" (Harris et al., 2013: 80).

the consequent prescribing switches to be identified. In each case the "new" medicine starts to replace the previous version as that nears the end of its patent life.

The first case, venlafaxine, involves the grant of a patent for the metabolite of a previously patented compound. The second case, omeprazole, involves the patenting of its isomer, esomeprazole. Both cases demonstrate substantial prescriber switching between the older, soon to be off-patent product, and the "new" product at the beginning of its patent life. The cost of granting patents for these close chemical variants is high.

Both cases also illustrate a second type of evergreening patent that effectively delays generic entry. The patent system regularly grants patents for combinations of known things, such as combining a known compound with a known release mechanism (e.g. immediate, delayed or extended) (Moir, 2013). With venlafaxine such a combination patent acted to delay generic competition by 2½ years. For omeprazole, combining the drug with an enteric coating delayed generic competition by eight years.

The two evergreening strategies are inter-twined. Delayed generic entry attributable to the method of delivery patents creates an extended period during which the originator company can introduce the "new" medicine into the market. Companies are thus able to get prescribers to focus on their "new" products, without any distraction from generic alternatives or declining prices. Because of this each case is presented as a whole before the issues involved are discussed in terms of their policy implications.

Table 1 The Cases – Key Characteristics

INN:	**Venlafaxine (+ desvenlafaxine)**		**Trademarks:**	**EFEXOR (+ PRISTIQ)**	
Owner:	Pfizer (previously Wyeth)				
Original API patent:	filed 6 December 1983, expired 6 December 2008.				
Last evergreening patent:	due to expire 18 August 2023.				
First market entry:	venlafaxine (Nov 1994)			desvenlafaxine (Feb 2009)	
Market life (years):	API:	14.0	with evergreening patents:		28.8
# evergreening patents:	8 granted	3 still active			
Litigation:	yes	patents revoked:	yes, partially		
2014 PBS market size	$A180.5m				
Key evergreening patent features:	extended release combination		metabolite		
INN:	**Omeprazole / esomeprazole**		**Trademarks:**	**LOSEC / NEXIUM**	
Owner:	Astra (previously owned by Hässle)				
Original API patent:	filed 11 April 1979, expired 11 April 1999.				
Last evergreening patent:	due to expire 7 May 2027.				
First market entry:	omeprazole (Dec 1988)			esomeprazole (Mar 2001)	
Market life (years):	API:	10.3	with evergreening patents:		38.4
# evergreening patents:	61 granted	10 still active			
Litigation	yes	patents revoked:	no		
2014 PBS market size	$A305.2m				
Key evergreening patent features:	enteric coating combination		isomer		

Note: *Still active date is COB 11 August 2015. Market size (outlays) data are for financial years.*

3.1. Venlafaxine and desvenlafaxine

Venlafaxine, a drug used to treat depression, is a serotonin-norepinephrine reuptake inhibitor, a class of drugs which first became available in the 1980s. It was approved to enter the Australian market on 16 November 1994. Marketed as EFEXOR, the effective monopoly period was just over 14 years – more than the US API average of about 12 years. There are

eight evergreening patents, but only two have delayed generic entry. One of several extended release patents (2003259586) delayed generic entry for venlafaxine by 2½ years. A chemical variant (patent 2002250058) allowed Pfizer to split the market into the original and "new" medicines, with the "new" market not subject to generic competition for a further potential 11 years.

3.1.1 Combination patents: extended release formulation

While venlafaxine was regarded as a useful new treatment option for depression, it was not without problems. A major side-effect was nausea, creating substantial non-continuance rates (Rudolph et al., 1998). The solution was an extended release (XR) formulation, smoothing out peaks and troughs in drug levels and thus sharply reducing the nausea side-effects. Once released on the market (May 1998), the XR version (EFEXOR-XR) quickly became the market norm – indeed Wyeth withdrew the previous formulation from the Australian Therapeutic Goods Register (ARTG).[4] This XR patent falls clearly within Machlup's definition of patent abuse.

Marketing approval for the XR version occurred quickly – a mere 14 months after the patent application was filed. The net impact of the XR patent was to extend the monopoly period by 8 years and 3 months, giving an anticipated effective monopoly period of over 22 years. The market for venlafaxine when generic entry was first attempted was $A151 million.[5] By 2014 the market for venlafaxine and replacement combined had reached $A180 million.[6]

The XR patent raises issues about patent standards. Why is combining a known compound with a known extended release mechanism sufficiently inventive to merit a patent? Why was use of extended release version not obvious, when it was peaks and troughs in blood plasma drug levels that created the strong side-effects? In both the USA and Australia the old synergy doctrine has been abandoned. That doctrine required that a combination of known things have an unanticipated effect or an outcome greater than the sum of the parts to be patentable.[7]

The technical specification for the first XR patent was highly specific – extended release by use of a hard gel capsule. This left it open to competitors to develop alternative extended release approaches. But then further XR applications were filed, one of which broadened the claims to *all methods* of achieving extended release. Although this last patent did not itself further extend the monopoly period, it strengthened Wyeth's ability to fend off generic competition during the extra 8 year monopoly period the first XR patent provided.

Sigma, a generics company, attempted to enter the market for XR venlafaxine in early 2009, shortly after the API patent expired. Wyeth sued for infringement of its broad XR patent, and

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[4] At that time withdrawal of an item from the Register meant that generic companies could not use the safety and effectiveness data for that drug to gain marketing approval for generic equivalents. This loophole has now been closed.

[5] Market entry estimates are based on total cost figures from annual compendia on PBS statistics, available at http://www.pbs.gov.au/info/browse/statistics#Expenditure.

[6] As at mid December 2015, data for financial year 2015 were not yet available.

[7] The synergy doctrine was overturned in Australia in 1980 by the High Court (*Minnesota Mining and Manufacturing v Beiersdorf* (1980) 144 CLR 253 at 117. The US Court of Appeals for the Federal Circuit made a similar ruling in 1984 (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572 (Fed. Cir. 1984)). The synergy doctrine allegedly still holds in Europe. Its effectiveness is a matter for empirical evaluation.

an injunction was granted on 3 June 2009.[8] Although the judge found prima facie evidence that the patent was invalid, he granted the injunction for two reasons: a view that it would be impossible to adequately recompense Wyeth for lost profits once generic entry had taken place;[9] and evidence about possible confusion among mentally ill and older patients as packaging and trademark names differ across producers. The EFEXOR-XR trademark and packaging thus played a key role in ensuring the grant of the injunction and the delay in generic entry. There was no discussion of the cost to taxpayer and consumers in the judgement.

Sigma appealed the decision and the claims in the patent which had restricted generic entry were declared invalid on 21 December 2011. Although the injunction was immediately lifted, the decision was appealed. The High Court refused leave to appeal, and it was finally safe for Sigma (and all other generic companies) to enter the market. These legal manoeuvres kept generics off the market for over 2½ years – until early 2012. This reduced the anticipated effective monopoly period from 22 to 16½ years.

It was clearly the broad XR patent which limited market entry, not the first hard gel capsule XR patent, nor the other evergreening venlafaxine patents that surrounded the API patent. Once generics entered the market, the price of EFEXOR-XR fell by a statutory 16 per cent. The cost to the Australian taxpayer of the delayed entry is estimated at $A85 million. This estimate is based on a very conservative assumption of a further 10 percent price fall 18 months later, and another 10 percent price fall 12 months after that.[10]

An interesting endnote to this part of the analysis is that Pfizer attempted to prevent the Commonwealth suing for the losses it incurred due to the delayed generic entry of venlafaxine XR. The most recent step in this saga is a Full Federal Court decision that the Commonwealth is entitled to sue to recoup these losses, but there is media speculation that the decision will be appealed to the High Court.[11]

3.1.2 Variant chemical specifications: the metabolite patent

Venlafaxine is metabolised into desvenlafaxine in the human body. Thus venlafaxine and its metabolite desvenlafaxine have identical therapeutic effects. Indeed desvenlafaxine has been assessed as offering no therapeutic advantage for any group.[12]

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[8] *Sigma Pharmaceuticals v Wyeth* [2009] FCA 595.

[9] While the mandated PBS price fall on generic entry is clear, there does not appear to be any mechanism to restore the price if generic entry occurs but then the disputed patent is found to be valid. This would not, however, prevent grant of commensurate compensation.

[10] Alphapharm, a generics company, estimated the cost of the 2 ½ year delay as $A209 million in its submission to the 2012-13 Pharmaceutical Patents Review (p. 6, http://web.archive.org/web/20130425142849/https://pharmapatentsreview.govspace.gov.au/submissions/).

[11] Commonwealth of Australia v Sanofi (formerly Sanofi-Aventis) [2015] FCAFC 172; https://pharmadispatch.com/news/court-backs-government-right-to-compensation

[12] In Australia this assessment was made by Pharmaceutical Benefits Advisory Committee (PBAC), Public summary document: Desvenlafaxine succinate, November 2008, (http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-11/pbac-psd-desvenlafaxine-nov08) and expanded on in "Your questions to the PBAC: patent expiry and 'new' drug approval", *Australian Prescriber*, 32:3, June 2009, p.63. NPS MedicineWise summarises the evidence on desvenlafaxine as "[t]here is no evidence that desvenlafaxine is more effective, safer or better tolerated than venlafaxine or other antidepressants." http://www.nps.org.au/publications/health-professional/nps-radar/2009/march-2009/desvenlafaxine.

It therefore seems surprising that desvenlafaxine was granted a patent. It is a metabolite of the known and patented chemical venlafaxine. Its existence was clearly known – indeed the metabolic action whereby venlafaxine is converted into desvenlafaxine would have been well known when the patent application was filed in February 2002.

Nonetheless not only was a patent granted, but so was an 18 month term extension. The patent covers desvenlafaxine and virtually any use of it as a medicine. When Wyeth applied for PBS listing, venlafaxine XR was still in patent. Wyeth was thus the price setter for both drugs, and set these so to ensure that the listing authority, the Pharmaceutical Benefits Advisory Committee (PBAC), would conclude that desvenlafaxine was cost-competitive, even though it provided no new therapeutic benefits. The PBS is not a limited formulary which means that as long as a proposed drug is cost-effective the PBAC **must** recommend PBS listing.

Desvenlafaxine entered the market in February 2009 (as PRISTIQ), around the time litigation over generic venlafaxine entry commenced. The owner, now Pfizer, had 2½ years during which EFEXOR-XR and PRISTIQ had no competition, due to the injunction. The marketing budget for PRISTIQ was so lavish that it attracted the attention of investigative journalists.[13] The "education" campaign was remarkably effective – by the time the first generic version of venlafaxine-XR entered the market in early 2012, 37 percent of prescriptions were for desvenlafaxine (Figure 1). As the price for the two drugs was similar during this period, there was no reason for doctors to resist the marketing pressure, despite the lack of any improved therapeutic effect for any group.[14] It is interesting, though, to speculate how Pfizer managed to convince so many doctors to change drugs when it had been unable to convince regulatory authorities of any improvement.[15] At the time of PRISTIQ's launch, a Vice President of Wyeth's Medical Affairs described PRISTIQ "an *evolutionary* advance that allows some advantages in individual patients."[16]

Once generics entered the venlafaxine market in early 2012, the economic impact of the prescribing switch began to emerge. The price of venlafaxine began to fall, while that for

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[13] Who point out that the initial "education" event stands out as the most expensive event in a database of 156,000 such events, see Clare Blumer, "Party like your drugs going generic", 31 May 2013, *The Global Mail*, (http://web.archive.org/web/20131216072420/http://www.theglobalmail.org/feature/party-like-your-drugs-going-generic/624/).

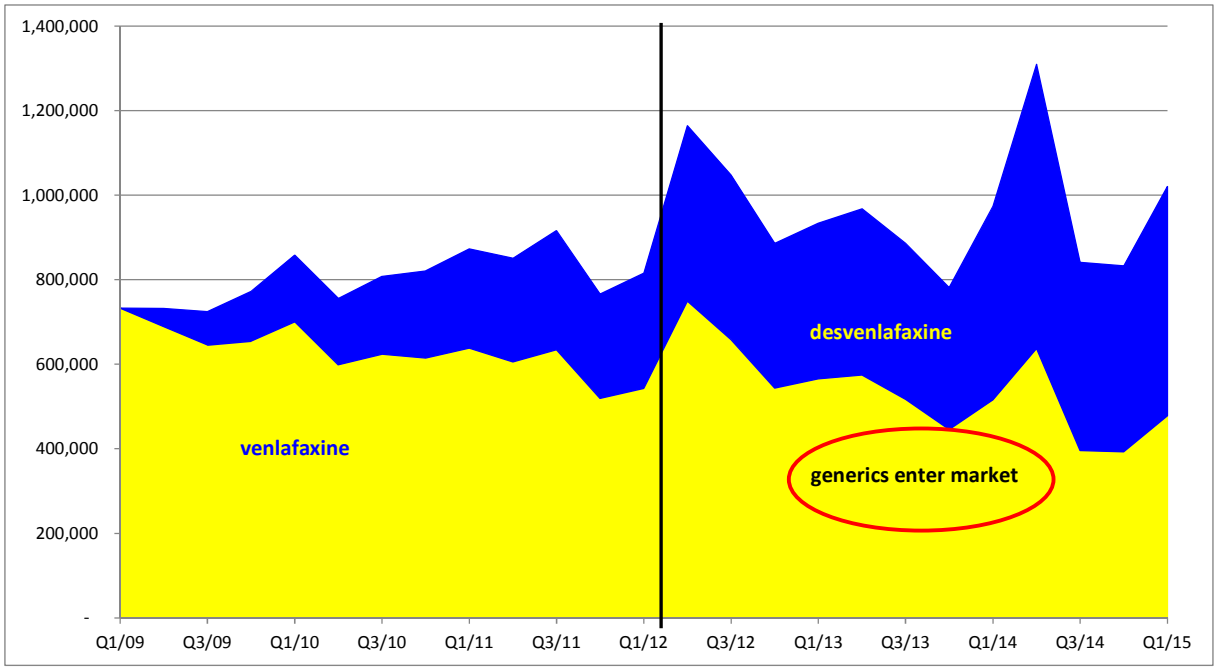
[14] The PBAC recommendation to list desvenlafaxine states "no evidence was presented to suggest that desvenlafaxine would offer an advantage for any particular patient group over the parent drug venlafaxine" (http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-11/pbac-psd-desvenlafaxine-nov08). A comparative study of venlafaxine and desvenlafaxine concluded that "[d]esvenlafaxine is similar to its parent drug venlafaxine in efficacy, safety, and pharmacologic parameters" (Sopko Jr et al., 2008: 1445).

[15] The material Wyeth provided to the European Medicines Agency (EMA) to gain marketing approval was nine studies, two of which included venlafaxine. The EMA notes that "the studies were not designed to compare the two medicines." Indeed Wyeth withdrew its European application for marketing approval as the EMA had found that "the benefits had not been sufficiently demonstrated and any benefits did not outweigh the identified risks" (Withdrawal Assessment Report for ELLEFORE: EMA/H/C/932: 22 January 2009, p.2 (at http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2010/01/WC500064247.pdf).

[16] http://psychcentral.com/blog/archives/2008/06/23/wyeths-dr-phil-ninan-on-pristiq/. This very subtle language seems designed to imply that desvenlafaxine is an improvement, without actually lying. Desvenlafaxine may be useful for patients with compromised liver function, and thus less ability to metabolise drugs. But this patient group is far short of 37 percent of patients but overall there are no reported clinical trials demonstrating this.

desvenlafaxine remained steady. Over time the price differential has increased substantially as competition between generics has driven down the price of venlafaxine XR.

Figure 1 Prescribing Shift: Venlafaxine and Desvenlafaxine[17]



Source: Calculated from data from https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml using the volume of prescriptions for the two main dosages of venlafaxine and the equivalent dosages of desvenlafaxine (8301X and 8302Y compared to 9366Y and 9367B). Data are for six monthly periods, based on Australian financial years. 09/1 is thus July-December 2008 and 09/2 is Jan-June 2009. Vertical axis is volume of prescriptions. The injunction against generic venlafaxine was granted in June 2009 and not lifted until late 2011.Generic market entry was February 2012.

With the entry of generics to the market, the true cost of patenting desvenlafaxine and listing PRISTIQ on the PBS emerges. The cost to taxpayers of the high volume of scripts for PRISTIQ in the 5 months of 2011-12 was $A3.2 million (Table 2). At that time the price reduction policy had an 18 month delay built in,[18] so there was little change in the cost to taxpayers in 2012-13 and 2013-14. But in 2014-15 there was a substantial widening in price differential as the price fall process for venlafaxine took fuller effect – the additional cost to taxpayers rose substantially to $47.2 million.

Possibly due to the substantial media interest in the desvenlafaxine case,[19] on 1 April 2013 desvenlafaxine was moved from the F1 to the F2 formulary.[20] This co-location in a "derivative therapeutic group" signals to prescribers that the two drugs are interchangeable. But it does not allow substitution at the dispensing level, thus limiting the generic share.[21]

[18] This delay has now been reduced to 12 months.

[19] Lateline ran a story on this on 15 May 2012, Drugs wrongly escaped pharmaceutical scheme, http://www.abc.net.au/lateline/content/2012/s3503662.htm.

[20] National Health (Listed drugs on F1 or F2) Amendment Determination 2013 (No. 2) https://www.comlaw.gov.au/Details/F2013L00573

[21] See http://www.pbs.gov.au/info/publication/factsheets/venlafaxine-therapeutic-group.

The change in therapeutic group appears to have had no impact on prescribing behaviour, and there has been no noticeable impact on the additional cost to the taxpayer.

Table 2 Venlafaxine and Desvenlafaxine: Price Differences, Volumes and Cost ($A)

	Venlafaxine price		Desvenlafaxine price		Extra cost to taxpayer per script	
	150mg	75mg	100mg	50mg	150/100mg	75/50mg
Late 2012	44.20	37.81	50.52	43.41	6.32	5.60
Nov 2013	37.92	44.31	41.65	48.62	4.31	3.73
Oct 2014	19.46	22.25	41.78	48.75	22.32	26.50
Nov 2015	18.81	17.29	36.06	41.91	18.77	23.10
Volume and total cost data						
	Desvenlafaxine scripts		Additional cost to taxpayer $A			
2011-12 year	1,215,836		3.2 million (5 months only)			
2012-13 year	1,492,669		8.9 million			
2013-14 year	1,834,980		7.4 million			
2014-15 year	1,942,010		47.2 million			
2015-16 year (est)	*2,058,531*		*43.3 million*			

Source: Price data from http://www.pbs.gov.au/medicine/ (various dates); volume data from https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml. Cost estimates are adjusted down by 10 per cent to allow for the price component that rewards the pharmacist for dispensing. 2015/16 estimates assume the same volume increase (6%) as 2014-15 and the 2014-15 50mg to 100mg script ratio.

Generic desvenlafaxine was approved in October 2014 but did not enter the market until mid 2015. The original desvenlafaxine patent was quietly allowed to lapse (in June 2010) though a patent for a salt is still in force. Why the desvenlafaxine patent was allowed to lapse in Australia is unclear as in the USA Pfizer is suing 11 companies for desvenlafaxine patent infringement.[22] There had been further publicity about the additional taxpayer cost of desvenlafaxine, but this was after the key patent was allowed to cease.

By November 2015 the price for 100 mg desvenlafaxine had fallen 16 per cent and that for 50mg by 13 per cent. But the cost to taxpayers of prescribing venlafaxine remained high – an estimated additional $A43.3 million for the current (2015-16) financial year. Over time the price should start to fall further, but as yet the very limited generic entry (just two companies) has had limited impact.

Had the desvenlafaxine patent not been granted, this questionable transfer from Australian taxpayers and patients to the new owner, Pfizer, would have taken place. The costs estimates in Table 2 are additional direct taxpayer outlays due to Pfizer's evergreening

[22] See http://www.robinskaplan.com/~/media/sdny/14-9/complaints/pacer-complaint-20140811-14-cv-06373.pdf?la=en and http://www.law360.com/articles/353660/pfizer-sues-11-rivals-to-defend-pristiq-patent for documentation on Pfizer suing for infringement for FDA approval of generic PRISTIQ (August 2014).

desvenlafaxine patent. The Australian pharmaceutical market is some two percent of the global pharmaceutical market. To date, Pfizer has received as estimated $A56.7 million additional income from Australia due to the grant of the patent for the metabolite venlafaxine. If Pfizer is able to achieve similar prices in other markets, its global returns from the switch to desvenlafaxine, based on an evergreening patent, are at least $A2,385 million.

3.2 Omeprazole and Esomeprazole

As with venlafaxine, omeprazole involves both a variant chemical structure –an isomer – and a patent for a combination of the known chemical omeprazole with a known delivery mechanism, an enteric coating.

Isomers, chiral centres and racemic mixes were discovered by Louis Pasteur in 1848. These compounds have a chiral centre made up of two forms (called stereoisomers, isomers, or enantiomers). These are mirror images of each other, in the same way that one's left and right hands are mirror images of each other. The racemate contains equal quantities of both isomers. It has long been understood that isomers behave differently biologically and that one isomer will usually be more pharmaceutically efficacious than the other, often with one isomer having all of the activity and the other isomer being inactive.[23] The most globally famous case of isomer patenting is the racemate omeprazole and its isomer esomeprazole – better known as LOSEC and NEXIUM.

A proton-pump inhibitor, in the human body omeprazole and esomeprazole form the same active substance which stops gastric acid production. They are used for the treatment of dyspepsia, peptic ulcers and reflux. In addition to the original API patent for omeprazole, there are 61 evergreening patents. But it was the patent for a combination of the known chemical omeprazole with a known delivery mechanism (enteric coating) which first kept generic competition at bay. During this period Astra-Zeneca introduced a "new" medicine – the isomer esomeprazole.

3.2.1 Combination patents: an enteric coating

Market approval in December 1988 gave Astra an anticipated 10⅓ year effective monopoly period for omeprazole (LOSEC) in the Australian market. The first evergreening patent was for an omeprazole salt – a chemical variant of the original API. Not only did this second patent expire five years after the original API patent, but Astra attached the five-year term extension for omeprazole to this patent, providing a ten-year rather than a five-year term extension. However this first evergreening patent was clearly not critical as generic companies attempted to enter the market in 1999 when the original API patent expired. A second evergreening patent, for an enteric coated version of omeprazole, was used to sue the new market entrants for infringement. Although this second evergreening patent only provided an additional 8 rather than 10 years of market exclusivity, it was upheld by the High Court and was thus effective in substantially delaying generic entry.

Both the Federal Court and then the Full Federal Court had determined the enteric coated patent to be invalid for want of any inventive step.[24] Effectively both lower court decisions

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[23] This discussion draws heavily on Alphapharm's submission to the Pharmaceutical Patents Review, pp. 20-21 (http://web.archive.org/web/20130425142849/https://pharmapatentsreview.govspace.gov.au/submissions/).

[24] *Aktiebolaget Hässle v Alphapharm Pty Ltd* [1999] FCA 628 (12 May 1999) and *Aktiebolaget Hassle v Alphapharm Pty Limited* [2000] FCA 1303 (9 October 2000).

held that the formulation in the patent was obvious to try with a reasonable expectation of success, which made it obvious. The High Court took a different view, strongly criticising the lower courts' approach. It upheld the enteric coated patent in a decision[25] that has been criticised as effectively removing any inventiveness requirement from the patent application process (Lawson, 2008). A similar decision five years later[26] also confirmed that if something was obvious to try with a reasonable expectation of success that did not make it obvious under patent law. The resulting "invention" should pass the inventiveness threshold for grant of an Australian patent.

The High Court's affirmation of an extraordinarily low inventiveness requirement was an expensive decision for Australian taxpayers and patients. Between May 1999 (when the original patent expired) and April 2007 (when the enteric coated patent expired), PBS outlays on enteric coated omeprazole were approximately $A3.1 billion.[27] With current pricing policies, the invalidation of the formulation (enteric coating) patent would have saved taxpayers an estimated $A 1.1 billion over these seven years.[28]

3.2.2 Variant chemical specifications: the isomer patent

As with venlafaxine, the injunction period (where the enteric coating patent was keeping generics off the market) saw the introduction of a "new" medicine – the isomer of omeprazole, marketed as NEXIUM. Astra introduced this isomer version into the global market in 2001 with a promotion budget of $US500 million (Goldacre 2012: 250).[29] In Australia, NEXIUM was approved for market entry on 28 March 2001, though the statistics on sales volumes indicate it did not actually enter the market until 2002. During financial year 2003 18 per cent of scripts were for the "new" medicine (Table 3). By 2014 the proportion of scripts for the "new" medicine – the isomer esomeprazole – was 77 per cent. There is little doubt that this massive switch in prescribing was helped by heavy marketing.[30]

The cost to taxpayers of this prescribing switch is estimated as $A48.6 million in 2003, rising to $A132.9 million in 2014 (Table 3). Over this 12 year period the total additional cost for esomeprazole was a massive $A1.8 billion in transfers from Australian taxpayers and patients to Astra-Zeneca. If similar price premiums and prescribing switches have been

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[25] *Aktiebolaget Hässle v Alphapharm Pty Ltd* (2002) 212 CLR 411 (*Astra*).

[26] *Lockwood v. Doric* [2007] HCA 21. The Australian patent office proposed legislative amendment to overturn this policy doctrine in 2009 (IP Australia, 2009a: 12-13). Due to submissions from unknown persons IP Australia stepped away from this proposed policy change (IP Australia, 2009b:12). The inventiveness test in Australia remains lower than elsewhere (see, for example, Summerfield, 2015).

[27] This is a conservative estimate, based on data for the years 1999 to 2006. This includes five months of 1999 which should be excluded, but excludes four months of 2007, which should be included. Total enteric scripts were less than 500,000 in 1999, but over 11 million in 2006.

[28] Volume data from https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml and average price data from annual statistical compendia, available at http://www.pbs.gov.au/info/browse/statistics#Expenditure. Assumes that prices for the May 1999 to June 2002 are the same as the average price for financial year 2003, and that enteric coated prices are the same as average omeprazole prices. Assumes prices initially fell by 16 percent then annually by 9 per cent.

[29] In 2011 Astra was still marketing NEXIUM heavily, reportedly spending US$478 million that year. See Gardiner Harris, Prilosec's Maker Switches Users To Nexium, Thwarting Generics, *Wall Street Journal*, 6 June 2002, available at http://online.wsj.com/article/0,,SB1023326369679910840,00.html (28 September 2013).

[30] As NEXIUM came on the market before the introduction of voluntary reporting of "education" expenditure by members of the industry group "Medicines Australia", marketing ("education") data are not available.

obtained from other markets, Astra-Zeneca has achieved an additional $A90 billion globally through the grant of this isomer patent.

Table 3 Esomeprazole: Market Share and Additional Cost Compared to Omeprazole

Financial year	Script volume	Omeprazole market share (by volume)	Total outlays ($A m)	Potential savings ($Am)	savings as % outlays	relative price esomeprazole
2002[a]	3,787,488*	97%*	207.7*	na	na	na
2003	5,226,762	82%	277.6	48.6	17.5%	118%
2004	6,160,820	67%	327.1	104.1	31.8%	114%
2005	6,774,218	59%	350.2	131.4	37.5%	120%
2006	7,229,619	53%	362.7	152.2	42.0%	126%
2007	7,637,053	47%	331.2	157.1	47.4%	124%
2008	8,152,696	41%	354.0	185.5	52.4%	120%
2009	8,307,512	33%	353.3	190.1	53.8%	136%
2010	8,316,690	30%	347.1	195.7	56.4%	135%
2011	8,072,154	29%	308.5	190.0	61.6%	122%
2012	7,925,986	28%	286.3	175.7	61.4%	123%
2013	8,210,606	26%	278.5	135.9	48.8%	170%
2014	9,013,589	23%	305.2	132.9	43.5%	200%

Source: Annual compendia of statistics (http://www.pbs.gov.au/info/browse/statistics#Expenditure). The report for financial year 2003 provides data on omeprazole, but not on esomeprazole.

a Estimated using the the percentage of esomeprazole scripts in 2002 from PBS statistics reports by PBS code (http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp).

The enteric coated patent kept generics out of the omeprazole market from 1999 to 2006. By the time generics were able to enter this previously lucrative market, Astra-Zeneca had achieved a 50 percent prescribing switch, closing half of the potential market to generic competitors even though the patent had expired. By 2014 the market for omeprazole had shrunk to just 23 per cent of the combined market for the two closely related medicines.

As with venlafaxine, just two of omeprazole's 61 evergreening patents were critical in extending the effective monopoly period. The key esomeprazole patent will not expire until 25 May 2018, some 11 years after expiry of the enteric coating patent. The overall effective market monopoly for these two closely related medicines is 29½ years. If the patent system

had a genuine inventive step, the only monopoly granted would have been for the original API patent. With a five year term extension, this would have provided an effective monopoly period of 15⅓ years.

4. Discussion of findings and policy lessons

These two cases confirm that the meaning of inventiveness under patent law falls far short of its ordinary meaning. Each case involves a patent where a known chemical is combined with a known release mechanism to gain an additional patent. There is a general assumption that pharmaceutical companies consider the best delivery mechanisms for the medicines which they offer to the public. These two cases suggest that this may well be a false presumption.

In the venlafaxine case the lack of consideration of the delivery mechanism led to poor patient continuation rates. In response the owner developed an extended release formulation. With much reduced side-effects, the XR version quickly became the market norm. In the omeprazole case an enteric coating was required to avoid rapid degradation in the acidic conditions of the stomach. Both changes in formulation were driven by market imperatives – without these changes the medicines would never have developed the volumes they actually achieved.

The policy question is why these variations to the previously patented compound merited additional twenty-year monopoly periods. In each case the “invention” combined a known (and patented) compound with a known delivery mechanism. There was thus no new knowledge delivered to society in exchange of the additional monopoly grant. In each case the change in delivery mechanism was an essential step in gaining market acceptance and the large sales volumes that would ensure a good return on the original investment. Clearly such developments would have occurred without the incentive of a second patent.

While one can define almost any new invention as a combination of known things, the desire to ensure genuine inventions are granted patents was achieved through a “synergy” doctrine. Under this doctrine combinations of known things were deemed obvious unless they produced an unexpected result or a result where the overall outcome was greater than the sum of the parts. This doctrine protected consumers and other innovative firms from the costs of relatively uninventive patents, while allowing patents for significant new combinations. Unfortunately this doctrine was overturned in Australia in 1980 and in the USA in 1984. It urgently needs to be re-instituted. Given the large number of process patents being granted, a new statutory requirement to require the use of the synergy doctrine should also apply to combinations of processes.

Turning to the patenting of chemical variants, the cases presented here involve a metabolite and an isomer. Both demonstrate that the inventiveness standard for grant of a patent is simply a marginal difference from what is known. In neither case was the second chemical structure previously unknown. Both should have failed the novelty test, and if not that, then the inventiveness test. The grant of additional patents for these closely related chemical compounds raises significant issues both about patent policy and about drug approval policies. In terms of patent policy the issues raised concern the quantum of inventiveness required for patent grant. In 2011 the Australian parliament was advised that this was “a significant advance in what is known or used”. These two patent grants show that this standard is not in use.

The cost of these four evergreening patents is substantial. The venlafaxine XR patent cost taxpayers at least $A85 million, though one generics company has estimated that the cost was closer to $A209 million. The estimated cost of the desvenlafaxine metabolite patent, to the end of June 2015, has been $A66 million. Overall then, these two evergreening venlafaxine patents led to an unwarranted transfer of at least $A150 million from Australian taxpayers to Pfizer. Current patent policy contains no mechanisms for the government (or other affected parties) to recoup these unwarranted profits. Indeed Pfizer has been fighting the Commonwealth's claim for recovery of losses simply during the injunction period for venlafaxine, one of its arguments being that it was the Commonwealth which issued the patent.[31]

The omeprazole patents had even higher costs. The delayed generic entry cost taxpayers an estimated $A1.1 billion over seven years. Over the 12 year period since the isomer based medicine esomeprazole came onto the market, the additional cost to the taxpayer from prescribing this higher priced alternative was $A1.8 billion.

These very substantial costs flow from the combined effects of current patent and pharmaceutical policies. If patents were only granted for significant advances over what is known and used, then none of the four patents would have been granted. Equally, though, pharmaceutical policy could have operated better to recognise that the two "new" medicines were not in fact genuinely new and should not have attracted such substantial price premiums.

In respect of desvenlafaxine, the current F1/F2 formulary approach has not yet operated to achieve equal prices, even though a regulation was made in April 2013 declaring the two medicines "should be treated as interchangeable on an individual patient basis." The creation of this single therapeutic group containing both medicines does not appear to have led to any change in prescribing behaviour. At the dispensing level the medicines are not treated as generic substitutes. What is interesting and surprising is that Pfizer has allowed the underlying desvenlafaxine patent to cease in Australia, though it is still enforcing it in the USA. There is no obvious reason for this. A search of the Pfizer Australia website finds no press release on generic desvenlafaxine.

The situation is more complex for esomeprazole. Although it is difficult to identify any head-to-head independent blind or double-blind trials of the two medicines, there is a theoretical argument that the isomer esomeprazole should be more efficacious that the racemate omeprazole. In effect, given the knowledge that one isomer is usually more efficacious than the other or the compound, there is a major issue in approving such medicines unless they are based on the more effective isomer.

Were patent standards increased such that an isomer could not be patented if the racemate or the other isomer had already been patented, drug companies working on the development of new medicines would know from the beginning that they would need to actively consider which chemical structure would produce the most effective medicine. This would provide greater protection to patients, as well as considerably reducing pharmaceutical outlays. If esomeprazole is in fact more effective than omeprazole – something we do not in fact know – then why was AstraZeneca happy to delay the

[31] This ignores the fact that the *Patent Act 1990* expressly states that nothing done under the Act "guarantees the granting of a patent, or that a patent is valid" (Article 20).

development of the isomer version until the omeprazole patent had almost expired? This question leads directly into questions about drug approval processes. While this is well beyond the scope of this paper, there are now so many look-alike or almost similar (if not virtually identical) medicines on the market, that the regulatory requirement to prove efficacy *only in comparison with a placebo* seems inadequate. As well as all the cases involving chiral compounds, there are many statins and literally dozens of low-dose combination oral contraceptive pills on the market.

Surely where there are already several closely related medicines on the market a new medicine should have to demonstrate relative as well as absolute efficacy. And where the two medicines are owned by the same company (either directly or through holding arrangements or licensing agreements) then there should be an absolute requirement for head-to-head efficacy comparisons. Pfizer's clinical trials for desvenlafaxine involved seriously depressed patients being given a placebo rather than the known and effective medicine venlafaxine. This seems seriously unethical.

At the beginning of this paper it was noted that it is uncontroversial to grant patents for truly new compounds – those involving a totally new active ingredient. Certainly such inventions would meet an inventiveness standard based on a "significant advance on what is known or used". But recent research has demonstrated with respect to pharmaceutical patents that the net cost to consumers from pharmaceutical patents is some six to seven times greater than the net benefit to producers (Branstetter et al., 2011; Chaudhuri et al., 2006; Dutta, 2011). Thus, like tariffs, subsidy would be a more efficient form of support.

It is clear from these two cases that current patent and pharmaceutical policies allow originator pharmaceutical companies to extract substantial premiums from the Australian market. These premiums go well beyond those already approved for genuine new medicines. Policy responses should include raising the inventiveness requirement in the patent system to the "significant advance" standard advised to parliament in 2011. They should also include changes to pharmaceutical pricing policies. Such changes should be designed to eliminate the higher prices paid for medicines such as desvenlafaxine and esomeprazole. The AUSFTA already links the patent system and the drug approval system. If a medicine already been approved for the PBS is based on a patented chemical, then prices for any "new" medicines based on close variants of that chemical should be constrained to the originally approved price. Drug approval processes also need improving. A particular focus should be to require clear head-to-head efficacy comparisons for closely similar medicines if these have the same ultimate owner/beneficiary.

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