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Policy challenges of nanomedicine for Australia’s PBS

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Abstract

All major pharmaceutical companies are currently investing significantly in the development of medicines with a nanotechnology component. Such research promises therapeutic drugs with greater efficacy and a wider range of clinical indications. Nanomedicines are just beginning to enter drug regulatory processes, but within a few decades could comprise a dominant group within the class of innovative pharmaceuticals. The current thinking of government safety and cost-effectiveness regulators appears to be that these products give rise to few if any nano-specific issues. This article challenges that proposition and seeks to explore what features of nanomedicines may create unique or heightened policy challenges for government systems of cost-effectiveness regulation. The Australian Pharmaceutical Benefits Scheme (PBS) is a key exemplar of the latter type of regulation in that it links expert scientific evaluation of cost-effectiveness with the pricing of PBS-listed drugs. In the current global financial crisis such systems are likely to become increasingly attractive and how they handle the demands made upon them by nanomedicines (including by application of a variation of the precautionary principle) is likely to be of considerable interest to policy makers worldwide.

What is known about the topic?

Nanomedicines are well recognised as a rapidly expanding field of research interest for major pharmaceutical companies. It is reasonably well known that nanomedicines are likely to soon be on the market but that there are safety concerns about nanomedicines which relate to some of their unusual properties. Data about any related risks is poor at this stage. The precautionary principle is a well established doctrine in safety regulatory assessments.

What does this paper add?

There have been few publications about the possibility of specific challenges from nanomedicines for cost-effectiveness regulators. This is the first paper to suggest that the precautionary principle should apply here in a cost-effectiveness as well as in the safety context.

What are the implications for practitioners?

Nanotechnology is likely to provide new medicines in key areas such as anti-neoplastics. These are likely to be expensive and heavily promoted. If approved by the PBS, much of the cost will be absorbed by the Australian taxpayer but with the consequence that PBS expenditure will continue to rise. Consideration of the precautionary principle in this context could influence prescribing habits of practitioners and hence PBS sustainability.

There is little doubt that within a few decades medicines with a nanotechnology component will comprise a large proportion of new submissions to Australia’s Pharmaceutical Benefits Scheme (PBS) (as well as similar government-coordinated health technology cost-effectiveness regulators around the world). Nanobiotechnology involves research into the interaction with living cells, proteins and biosystems, of engineered ultra-small particles (for example quantum dots, oxides, nanocomposites, fullerenes and carbon nanotubes [CNTs]) having at least one dimension less than about 100nm (0.00001 cm).1 Nanotechnology research is particularly important to contemporary diagnostic imaging and devices, the latter nanotechnology market estimated to be worth about $US4 billion in 2009.2 Nanobiotechnology medical devices are being developed, for example, with applications in neurosurgery3 and cardiac surgery.4

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It is uncontroversial to state that nanotechnology is an expanding area of pharmaceutical research and development globally. More than two hundred drug companies have active research programs in nanomedicine. Such programs are mostly predicated on nanotechnology having a powerful enabling function that will enhance the efficacy and market competitiveness of existing products. Nanotechnology offers particular value in this context as a drug carrier system. Peptide nanotubes, for instance, have been investigated as the next generation of antibiotics, and as immune modulators. Anti-cancer drugs are another particularly strong field for nanotechnology research. Ten drugs involving nanotechnology have already been approved by the United States Food and Drug Administration (FDA) for human use.

In Australia, nanomedicine is a small but emerging industry sector. Starpharma, for example (in partnership with US-based Dendritic NanoTechnologies and with Australian Government as well as US National Institutes of Health funding) is developing VivaGel™ (SPL7013 Gel). This is an HIV-prevention nanodendrimer-based microbicide synthetic polymer vaginal gel that binds to glycoproteins on the surface of HIV and thus prevents, in a dose–response manner, HIV binding to receptors on T-cells. VivaGel™ was the world’s first nanodendrimer-based drug approved for human trials by US FDA. pSividia is an Australian company that has developed BrachySil™, a nanostructural, porosified, biosilicon platform technology for controlled drug delivery, and already has a licensing agreement for it with a US company based in China. A variety of drugs already listed on the PBS utilise “first generation” nanotechnology manufacturing and drug delivery processes. Some such PBS nanotherapeutics utilise a new “milling” process patented by Elan Pharma International under the name of NanoCrystal technology. These drugs include Rapamune® (sirolimus), Megace® (megestrol acetate) and Emend® (aprepitant).

Abraxane™ (paclitaxel albumin-bound particles) is a nanotechnology-based anti-neoplastic agent. It has become the first explicitly declared “nano” drug to come before the Australian Therapeutic Goods Administration (TGA) for safety, quality and efficacy regulatory approval. If successful before the TGA it will seek to be listed on the PBS. Abraxane, as with many nanotherapeutics, constitutes a nanoreformulation of a pre-existing medicine, with the active ingredient paclitaxel being an antimicrotubule chemotherapeutic agent from the taxane group.

The preceding examples represent the early stage of a surge in nanomedicine products that will soon be confronting safety and cost-effectiveness regulatory assessors worldwide. Whenever a new technology, such as nanotechnology, promises to produce a new class of medicines, academic commentators have a tendency to inflate the unique problems it will create for patients, practitioners and regulators. Yet, in the case of medicines based on new genetic technologies, moral and safety concerns have already led to a moratorium on germ-line gene therapy as well as other forms of inter-species and reproductive genetic medical research — here, the application of the precautionary principle is generally regarded as appropriate. Should a similar degree of regulatory precaution apply to cost-effectiveness analyses of nanomedicines?

Perhaps it is because the nanotechnology revolution is following so closely upon the heels of the thorough public debate about the promise and risks of gene-based medicine, that many claims about nanomedicine presenting particular prob-

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lems for regulators are perhaps being too readily dismissed. This article examines whether this is indeed the case and what should be done if it is. It begins by highlighting some features of the contemporary Australian drug regulatory approval process for which nanomedicines are likely to create challenges.

Australia’s two-tier (safety and cost-effectiveness) regulatory process is well described in other articles in this issue of *Australian Health Review*. Only those features most pertinent to nanomedicines will be highlighted here. Australia’s addition of a system for scientifically evaluating therapeutic significance to reimbursement arrangements premised on the application of central government buying power has been a major Australian contribution to international pharmaceutical regulation. In 1999 the Pharmaceutical Benefits Advisory Committee (PBAC) of the PBS was the only government-coordinated “reimbursement agency” in a developed nation pharmaceutical market that conducted an in-depth, science-based cost-effectiveness review of all proposed therapies. Recently, nations such as South Korea have sought to adopt a variation of the PBS process (in that case through a specific request in bilateral trade negotiations with the United States) as a model system for better ensuring the effective and equitable distribution of medicines. The United Kingdom National Institute for Health and Clinical Excellence, the Canadian Expert Drug Advisory Committee and the Canadian Agency for Drugs and Technologies in Health are examples of institutions providing recommendations about medicines cost-effectiveness that are not directly linked to a government pricing negotiation. Several governments, including even the United States, presently have a strong interest in adopting variations of Australia’s national pharmaceutical cost-effectiveness model.

**Australian safety and cost-effectiveness regulation: four challenges from nanomedicines**

All medicines or medical devices before being marketed in Australia must apply for safety, quality and efficacy evaluation under the *Therapeutic Goods Act 1898* (Cwlth). Amendments to the Act in 1999 also required “timely availability” to be considered as part of this process. Approved therapeutic goods are entered on the Australian Register of Therapeutic Goods (ARTG) as a precondition to being marketed in Australia.

After ARTG listing, a supplier of a prescription drug may apply to the federal Department of Health and Ageing to have that product listed on the PBS. PBS listing is critically dependent on a recommendation by the PBAC as assisted by the Economics Sub-Committee (ESC) and the Drug Utilisation Sub-Committee (DUSC).

The PBAC is required, in making its PBS listing recommendation to the Minister, under section 101 of the *National Health Act 1953* (Cwlth) to consider “… the effectiveness and cost of therapy involving the use of the drug … including by comparing the effectiveness and cost of that therapy with that of alternative therapies” (section 101 (3A)). Where the alternative is “substantially more costly” the PBAC shall not recommend it for listing unless “for some patients” it represents a “substantial improvement in efficacy or reduction in toxicity” over those alternatives (s3B(a)). A positive recommendation from the PBAC also (since amendments in 2007) must be accompanied by a specification as to whether the drug is “interchangeable on an individual patient basis” (section 101 (3BA)).

In August 2007 the *National Health Amendment (Pharmaceutical Benefits Scheme) Act 2007* (Cwlth) created two PBS pricing formularies. F1 comprises single brand, mostly patented and so-called innovative drugs, and F2 comprises multiple brand, mostly generic medicines (new section 85AB and 85AC into the *National Health Act 1953* (Cwlth)). The then Minister for Health and Ageing stated that the role of the PBAC, in assessing cost-effectiveness and cost minimisation and then advising the Minister on the listing of drugs on the PBS, would not be affected by the F1–F2 legislation.

The above basic legal requirements of the PBS process arguably create four main points where nanomedicines may create unusual challenges.
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These will be examined sequentially in the rest of this article. The first relates to comparisons of a nanomedicine on effectiveness and cost grounds against existing therapies (s 101(3A)). The second concerns the requirement for the supplier of a substantially more costly nanomedicine to establish its substantial reduction in toxicity over comparitors (s 101 3B(a)). The third concerns the recently introduced need for the PBAC, upon PBS listing, to specify whether a nanomedicine is “interchangeable on an individual patient basis” (s 101 (3BA)). The fourth point concerns the heightened potential for anti-competitive behaviour associated with preferential F1 status given the unusual capacity of nanomedicines to make claims to “innovation”.

1) Comparing effectiveness and cost of nanomedicines against alternatives

Pharmaceutical companies seeking to list a drug (including a nanomedicine) on the PBS schedule must submit a proposal to the PBAC in accordance with the Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (the Guidelines). All such submissions involve a process referred to as “translation”, involving: a) “applying” the clinical evidence to the proposed population — Australians; b) “extrapolating” the clinical evidence over a longer time frame (for a cancer treatment, for example, “full life expectancy”, a period longer than that of most “pivotal” clinical efficacy trials); and c) transforming the clinical cost-effectiveness data (often based on “surrogate” physiological outcomes) into “patient-relevant outcomes” such as quality adjusted life years (QALYs) gained. Both Abraxane and products containing Elend's NanoCrystals have direct clinical comparators. For Abraxane it is the fellow taxane Taxol. Can the PBAC be sure of receiving randomised clinical trial (RCT) data that comply with the translation process and involve such competitors?

The main challenges nanomedicines will create here for the PBAC relate to the fact that it is unlikely manufacturers will provide data showing effectiveness over a long timeframe in terms of QALYs or in a head-to-head RCT against an existing marketed product for the same indication. Under Section B of the Guidelines, pharmaceutical companies must provide all clinical trials relevant to the listing, not merely those considered “pivotal” (an important difference with the TGA process). Failure to disclose all studies, whether head-to-head, RCT or where a placebo is the alternate treatment, may create a fatal flaw for a submission. Where a sponsor seeks to exclude a study it must still list it in the table and provide an explanation as to why it should not be considered by the PBAC. Yet, a requirement that RCTs be disclosed is different from a Guidelines statement about the type of RCTs that should be conducted. Similarly, the Guidelines provide that, in circumstances where no comparator treatment is PBS listed the “current standard care” is to be the objective reference point. But this also falls short of a directive that RCTs (including those involving nanomedicines) be conducted involving that current standard care.

One particular challenge here will be whether for a nanoreformulation of a drug already listed on the PBS head-to head RCTs comparing effectiveness against that listed original, rather than placebo, are required. Manufacturers of nanomedicines, protective of their investment in a new field with many unresolved safety issues, will particularly be reluctant to undertake such RCTs as it might heighten competitor claims their new product is merely an F2-bound nanogeneric, rather than a technologically innovative product entitled to much more lucrative F1 status.

Another factor will be that submission prices for nanomedicines are likely to be particularly high in order to recoup substantial research and development costs. It also may be unusually difficult for companies manufacturing nanomedicines to enroll human subjects into such RCTs: the incompletely understood risk profile of nanomedicines (a problem that is likely to remain unsolved for some time) may make patients reluctant to remain on nanomedications long term. Hence, there may be a heightened tendency for nanomedicine RCTs to use more rapidly acquired data such as physiological parameters (for example reductions in biomarkers) as outcome measures.
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2) Costly nanomedicines: establishing substantial reduction in toxicity

Section 3B(a) of the National Health Act 1953 (Cwlth) provides that where the alternative is “substantially more costly” the PBAC shall not recommend it for listing unless “for some patients” it represents a “substantial improvement in efficacy or reduction in toxicity” over those alternatives. Highly reactive and mobile engineered nanoparticles (ENPs) may present unique health risks when used in medical applications.25 Yet, there are currently no effective methods to monitor ENP exposure risks.26

The current literature on nanotoxicology strongly suggests a level of agreement about adverse effects of small size, surface area, insolubility and kinetics of ENPs at the cellular level.27 Some ENPs have been shown to preferentially accumulate in mitochondria and inhibit function; others may become unstable in biological settings and release elemental metals.26

The US FDA appears to have assumed that proven macroscale safety translates to similar findings for a nano version of the same product.28 A nanoparticulate reformulation of an existing drug, for example, has been deemed by the FDA to be bioequivalent and to permit safety regulatory approval under the Special Protocol Assessment process.29 Thus Abraxane, a nanoreformulation of paclitaxel, could claim a reduction of toxicity, for example, because its form as an injectable suspension evades the hypersensitivity reaction associated with Cremophor EL, the solvent used in the original macro compound. A major challenge for regulators here is that nanomedicine toxicological effects cannot readily be predicted by extrapolation from macroscale equivalents. Silver nanoparticles, for example, which have potent antibacterial effects (encouraging their use in wound dressings) have been proven to demonstrate cytotoxicity due to their production of free radicals.30

Another great concern is that certain ENPs may create specific health problems with delayed latency and lethality that resemble asbestosis.31 The existing toxicological paradigm for asbestos-induced cancer of the lung and pleura (mesothelioma) highlights the necessity for sufficient concentrations and biopersistence of thin (less than 3μm) and long (greater than 20μm) fibres.32

Considerable concern was thus aroused by a recent paper that exposed the mesothelial lining of the body cavity of mice (as an experimental surrogate to the mesothelial lining of the lung) to 50μm doses of long fibre amosite or brown asbestos, as well as multiwalled carbon nanotubes (MWCNTs), ranging from an average sample size of 1μm to 56μm in length. One hypothesis was that such cylindrical objects readily enter cells by receptor-mediated endocytosis harnessing the protein clathrin. Only the long asbestos and MWCNT fibres elicited the polymorphonuclear leukocyte activation, protein exudation and granuloma formation characteristic of the inflammatory response.33

Another challenge is that most contemporary nanotoxicological studies focus firmly on examining the interaction with biological systems of the manufactured surface of ENPs, not on their formation of a fluxing corona (through an aggregate of varying kinetic on/off rates or equilibrium binding constants) involving many of the thousands of different proteins that would immediately aggregate around ENPs in human plasma.34 How this ever-shifting protein corona associates with ENPs is a critically important but largely unexplored factor in how they enter and leave cells and hence their toxicological and therapeutic fate.35 The coating of proteins over an ENP in different organ compartments or cellular environments, for example, may transmit altered biological effects due to altered protein conformation, exposure to novel proximate amino acid residues or epitopes, perturbed function and downstream cellular signalling pathways (due to structural effects or local high concentration) and avidity effects from close spatial repetition of the same protein.36

A recent Parliamentary Inquiry in New South Wales has called for mandatory labelling and for nanomaterials to undergo separate safety testing from their bulk equivalents.37 The report recognised that the unique properties exhibited by many nanomaterials raise the question of whether
the existing regulatory frameworks for the management of products incorporating chemicals are sufficient to cover the health, safety and environment concerns potentially posed by nanomaterials. During the Parliamentary Inquiry, the Committee found the most frequent concern expressed about the current regulatory frameworks was the fact that nano versions of existing chemicals are not automatically assessed as new chemicals. Recommendation 1 of the report addressed this concern, suggesting that, “the New South Wales Government recommend that nano versions of existing chemicals are assessed as new chemicals”. Application of such recommendations will need federal coordination to be effective, but some such changes are inevitable and they must impact on assessments of the toxicity of nanomedicines, further highlighting the unusual challenges such drugs will create for this aspect of the PBAC process.

One way forward for the PBAC in the face of such uncertainty about the toxicological data associated with nanomedicines is to explore application of a variation of the precautionary principle. This emerged as a theme of regulatory policy in Germany during the 1970s and spread through the international arena as a philosophical challenge against traditional policy-making. Its core idea was that lack of scientific certainty about the potential harm of a product or process being evaluated by regulators should not be used as an excuse to delay measures protecting the public or the environment from harm and should allow marketing of such a product to be delayed, restricted or have its risks notified to the public. The precautionary principle has since then been incorporated into a number of fields of environmental protection, with variations in formula, including the protection of the ozone layer, climate change, biological diversity, fisheries management, and extending even to the protection of human health generally, including food safety. The development and application of the precautionary principle have not been free from criticism. Some commentators argue, for example, that regulatory application of a precautionary measure may have adverse effects, rendering protective measures hazardous in themselves to the environment or human body. Others warn that it may well prevent development of new technologies that may serve to alleviate the environmental harm.

The precautionary principle is not a monolithic concept, but rather sets a framework within which precautionary measures may be taken. The way in which the precautionary principle may apply to cost-effectiveness regulatory consideration of nanomedicines will depend on the correlation between the nature and seriousness of the risk as well as the kinds of remedies to be made available. For example, if the potential toxicological risk from nanomedicines involves serious and irreversible threats to human bodies and environment, strong regulatory measures, such as refusal of TGA approval, or of PBAC listing, can be justified even in the face of such scientific uncertainty. On the other hand, if the potential toxicological risk to some patients from a costly nanomedicine is found by the TGA to be not so serious as to prevent marketing approval, it could still be reasonable for the PBAC to impose a precautionary measure as a condition of PBS listing. This could entail, for instance, specified ongoing post-marketing toxicological and usage investigations with reporting requirements to the PBAC.

3) Nanomedicines: interchangeable on an individual patient basis?

A positive recommendation from the PBAC (since amendments in 2007) now must be accompanied by a specification as to whether the relevant drug is “interchangeable on an individual patient basis” (s101 (3BA) National Health Act 1953 (Cwlth)). This at first looks to be an impossibly vague standard, it being very difficult to see how any nanomedicine, given that class of drugs’ unusual chemical properties and inadequately understood toxicity risks, could be completely interchangeable in terms of the preferences of every individual patient.

Perhaps one solution to the ambiguity inherent in s101(3BA) is to read its words in the context of an overarching presumption (derived from a pur-
positive judicial interpretation of s101 of the National Health Act 1953 (Cwlth)) that the PBAC evidence-based process should remain as rigorously objective as possible. Such a presumption would be naturally inconsistent with any reading of s101 (3BA) that required a PBAC listing recommendation to summarise necessarily imprecise (no standardised criteria) and subjective individual patient preferences, for example comparing nanomedicines with any marketed comparator.

It is possible to advance an interpretation of the words in s101(3BA) consistent with the above presumption (supporting interpretations of ambiguities in the National Health Act 1953 (Cwlth) that most respect the scientific integrity of the PBAC process). This interpretation is that, rather than representing a move away from the objective standard of biological equivalence, s101 (3BA) simply requires the PBAC, generally (and in the case of nanomedicines), to specify whether the newly listed product falls within some limited preexisting category discerned from past documented use of this phrase by the PBAC. Supporting this limited interpretation is the fact that the requisite legislation included no definition of the words “interchangeable on an individual patient basis”. In other words, if the legislature had decided this phrase, never before used in the National Health Act 1953 (Cwlth), did not require explanation, a judge is entitled to assume that was probably because the Parliament knew the words could readily be determined by reference to existing PBAC documents.

In essence, the argument here is that it should not matter in terms of the applicability of the PBAC cost-effectiveness process to nanomedicines whether or not any one or all of them is classified as “interchangeable on an individual patient basis” with another compound. If they are so classified under s101 (3BA), then that determination would apply to only a very small pool of the total number of patients who might use the drug. If a nanomedicine is not so classified, then no conclusion can be drawn from that alone about wider issues of its comparative cost-effectiveness. In summary, an s101(3BA) determination, both in general and for nanomedicines, cannot be presumed to undermine the objective standard of biological equivalence or significantly erode the scientific objectivity of the PBAC process as established by s101 of the National Health Act 1953 (Cwlth).

4) Preferential F1 status and nanomedicines’ unusual claims to innovation

Until the F1-F2 scheme is abolished or substantially modified to better cohere with the principles of the National Medicines Policy, PBS prices will now be influenced by which formulary a drug is in.41 It is likely that manufacturers of nanomedicines will expect all such drugs to be listed on the PBS at the submission price and in the F1 category. They would resist, for example, Abraxane, on initial submission being cost-effectiveness-compared against other paclitaxel-based medicines (under the previous unitary PBS it may have been price referenced if unable to establish superior cost-effectiveness).

Partly this is due to industry assumptions that the F1 category was specially created to reward innovation (outside the patent system) as was required by Annex 2C of the AUSFTA. Yet such a view is not consistent with Australia’s overtly expressed legitimate expectations from that agreement. Australia’s interpretation of the constructive ambiguity of “innovation” defined the concept more as “health innovation” (the national benefit proven to arise from marketing the product) rather than “marketing innovation” (the degree to which lobbying and advertising can make a case for its technological innovation).19 This being so, it is conceivable that, despite a manufacturer’s claims to “technological or market innovation” for a nanogeneric medicine, it could achieve an F2 classification if comparative cost-effectiveness (“public health innovation”) could not be established. This is assuming, of course, that safety concerns had been adequately addressed.

Similarly supporting such a conclusion is the presumption that any interpretation of the National Health Act 1953 (Cwlth) and related PBAC guidelines should take into account the
overall importance (as stated in s101) of maintaining the scientific rigour of the PBAC assessment process and the purpose of ensuring value in the expenditure of public money under the PBS scheme.

Thus, even taking into account the costs to the Abraxis company in developing its nanoparticle albumin-bound (nab®) technology, a recommendation from the PBAC — for PBS listing with an F2 classification — is feasible and without further information would not legitimately form the basis for an appeal to the Independent PBS Convenor.42 This outcome would additionally square with considerable doubts that have been expressed by overseas commentators upon the relevant scientific evidence over the minimal therapeutic improvement provided by Abraxane.43

The capacity to list nanomedicines in the F2 category will be important, as it is expected that nanoreformulations of older drugs will appear on the market earlier than novel “blockbuster” nano-based drugs.44 Such “me-too” or “incrementally innovative” drugs may offer only a minor (if any) proven therapeutic benefit to the Australian population despite their novel nanotechnological base.45

**Conclusion and recommendations**

In summary, this review has suggested that unresolved toxicity issues will provide the main challenge that the PBS evidence-based system of cost-effectiveness analysis will face, under various categories, in relation to nanomedicines. Claims to F1 status based on “abstract technological” or “market-based”, rather than evidence-based “public health” claims to “innovation” will be another unusually problematic area. Establishing “interchangeability on an individual patient basis”, however, may not be as challenging as first might have appeared, particularly if that categorisation is shown to relate to a very specific and limited, previously defined category of PBAC data.

To be more specific, it would be facile to suggest that the toxicity issues raised by this expensive class of medicines for the PBAC process may be rapidly resolved by more toxicological research. Both government and industry are aware of the need for such research, but on most estimates it will take over a decade to answer many of the core toxicological questions about nanomedicines. In the interim, the precautionary principle could have an important role to play in PBAC determinations.

It is unclear how the standard of “interchangeable on an individual patient basis” relates to the traditional objective standard of biological equivalence. But it is even harder to discern what benefit the Australian community gains from the insertion of this potentially vague and subjective criterion in the mix of PBAC recommendations. It is strongly recommended that this phrase in s101 (3BA) of the *National Health Act 1953* (Cwlth) be repealed. To do so would only enhance the scientific rigour of the PBAC process and have no obvious deleterious impact on any aspect of the PBAC process.

Finally, nanomedicines, particularly with their claims to “technological” or “market-based” (but not necessarily evidence-established “public health”) “innovation”, provide a particularly strong case study supporting repeal of the 2007 amendments to the *National Health Act 1953* (Cwlth) fracturing the PBS formulary into F1 and F2 categories. Its constitutional and legislative history establishes clearly that the PBS system is set up to ensure equity and community health value for public expenditure on medicines. That must remain the dominant criteria for PBS listing, not manufacturers’ assertions of technological novelty potentially significantly dissociated from scientific evidence of national benefit.

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**Competing interests**

The author declares that he has no competing interests.
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21 Therapeutic Goods Act 1989 (Cwlth), s 4.


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