HEALTH CONSUMERS' COUNCIL

YOUR VOICE ON HEALTH

Submission to the Senate Community Affairs Legislation Committee inquiry into the Therapeutic Goods Amendment (2016 Measures No. 1) Bill 2016

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Executive Summary

The Health Consumers Council (WA) notes that major thrust of the *Therapeutic Goods Amendment (2016 Measures No. 1) Bill 2016* is to amend the *Therapeutic Goods Act 1989* (the Act) to support the implementation of eight key recommendations (Recommendations 3, 13, 15, 24, 27, 41, 42 and 47) of the Expert Panel Review of Medicines and Medical Devices Regulation (the Review). The Review was primarily established to "identify areas of the regulation of medicines and medical devices which could be streamlined, while maintaining the safety and quality of therapeutic goods available in Australia".[1]

The Health Consumers' Council (WA) Inc (HCC) accepts that there are potential benefits to consumers in 'streamlining' the approval for market of medications that offer a significant improvement over currently available medicines where the safety and efficacy of medications can be assured. However, the HCC notes significant past failings of the Therapeutic Goods Administration (TGA) processes to protect the health and safety of consumers.

We note most of the recommendations identified for implementation (3, 13, 15, 24, 41, 42 and 47) will advantage industry by providing alternate approvals processes and appeals rights to industry. We believe similar appeal rights (to that extended to industry via recommendation 47) should exist for third parties who oppose the licensing. We are not opposed to any of these measures outright but contend the processes of licensing, subsidising and monitoring pharmaceuticals in Australia are far from transparent and effective. We believe addressing these shortcomings should be the first priority of the parliament.

While the main focus of this Submission relates to regulation of medicines, HCC would like to reference medical devices by highlighting the current new Senate Inquiry into the number of women Australia who have had transvaginal mesh implants and related matters. The Terms of Reference of this Inquiry relate to "The Therapeutic Goods Association's: role in investigating the suitability of the implants for use in Australia; role in ongoing monitoring of the suitability of the implants; and knowledge of women suffering with health problems after having transvaginal mesh implants."[2]

While HCC will be providing a full submission to this Inquiry, we take the opportunity to highlight the importance of having third parties able to oppose licensing of therapeutic goods as well. For the women who have been adversely affected by having urogynaecological mesh inserted, they are unable to have it fully removed in Australia. Better systems for reporting adverse outcomes to medical devices, and having avenues of appeal is an important community right.

When licensing drugs for marketing the TGA relies on research funded and controlled by pharmaceutical companies. These enables pharmaceutical companies to 'cherry pick' evidence. In the most extreme cases, like Vioxx and Pradaxa, patients die. Similarly, privacy provisions in the *Health Act (1953)* effectively exempt dealings between pharmaceutical companies and Commonwealth Government agencies involved in determining which drugs are subsidised by the PBS from Freedom of Information requirements.

The TGA's post-market monitoring of drugs is equally as problematic. Voluntary reporting, inadequate disclosure, and a lack of systematic analysis of adverse events results in an overly optimistic perception of the safety and efficacy of many drugs currently on the market. We are supportive of recommendation 27 on post-market monitoring and encourage the committee to incorporate the reforms we identified below into their recommended response.

The specific reforms we seek were first identified to the parliament in a 2014 HCC submission to the Senate Select Committee on Health. In that submission, we identified seven potential reforms that would encourage greater transparency in regards to the licencing and post market monitoring of pharmaceuticals in Australia.[3] We also made a similar submission to the Review and participated in consultations.[4] We note however, that

apart from acknowledging our submission and participation our submissions appear to have had little impact.

We trust the committee will consider the seven proposed reforms (listed below) which are discussed in greater detail in the following pages:

1. Reforming Commonwealth Freedom of Information legislation to end the entitlement of corporations to rely on privacy provisions originally intended to protect the health records of individuals. (see page 10)

2. Require full public disclosure of all relevant safety and efficacy data (with protections for intellectual property and commercially sensitive information) of all evidence regarding pharmaceutical products approved for market and/or subsidised in Australia. (see page 11)

3. Prevent cherry picking of favourable results by requiring pre-registration of all new research that may be later used to support the TGA licencing and PBS subsidisation of pharmaceutical products in Australia. (see page 11)

4. Strengthening Consumer Medicine Information (CMI) requirements so that:

    - Every warning currently included in information to prescribers is also on the CMI
    - It should also be mandatory to include a CMI inside medication packaging.
    - Putting a brief summary of the most serious (boxed) warnings on the outside packaging of drugs so consumers are aware of very significant risks. (Currently boxed warnings are often only highlighted on information made available to prescribers and are not seen by consumers.) (see page 13)

5. Make adverse drug event reporting to the TGA for a specified range of serious reactions (suicidal ideation, strokes, psychosis etc.) mandatory and regularly publish full de-identified details on the TGA website. (see page 14)

6. Require full public disclosure of pharmaceutical industry funding sources for clinicians, researchers, patient groups, advisory board members and members of committees involved in regulatory and policy development processes. (see page 15)

7. The Commonwealth Government should commission or conduct research into the incidence and impact of 'off label' prescribing. The research should concentrate on the health impacts of off label prescribing and the extent of PBS subsidisation for the off-label use of medications. Based on the outcome of this research the Commonwealth Government may consider if over time it is worth encouraging 'off label' prescribing to become 'on label'. This could be achieved by gradually enforcing PBS subsidisation of medications to those prescribed within the approved guidelines. This may encourage pharmaceutical companies to apply to the TGA to expand the range of authorised uses of their products and would help ensure that prescribing practices are supported by robust evidence. (see page 16)

A significant barrier to these necessary reforms may be the influence of the Pharmaceutical Industry and their peak body, *Medicines Australia*. Big Pharma's enormous economic resources and political skills have enabled them to dominate, virtually uncontested, the processes of licencing and subsidising their products in Australia. Without political leadership on these issues Australians will continue to pay too much, be denied fully informed consent and be exposed to unnecessary risks. We trust committee members will provide that leadership.

Introduction -What are the problems with the current system of licensing and regulating post market the safety and efficacy of medicines in Australia?

The market for medication is globally integrated. National drug safety regulators often rely on international research. There have been numerous high profile examples both internationally and within Australia of the consequences of the failure of regulators to protect consumers.

Vioxx, Pradaxa and other safety marketing failures in Australia and Internationally - In 2004 after causing an estimated 60,000 deaths worldwide primarily from heart attacks and strokes, Merck pharmaceuticals bestselling arthritis drug Vioxx was withdrawn from sale worldwide. Prior to that Vioxx's manufacturer Merck had 'mounted a ghost-writing campaign' to promote Vioxx. Ninety-six articles were published, some of which omitted to mention the deaths of patients who participated in clinical trials of the drug.[5] Not only did it promote dishonest conduct, Merck had 'drawn up a hit list of "rogue" researchers who had criticised Vioxx [who] had to be discredited and 'neutralized'.[6] [7]

Vioxx is not an isolated example of a drug company concealing evidence relating to the safety of one of their drugs. Recent revelations that Boehringer Ingelheim, the maker of anti-coagulant drug Pradaxa, had withheld some of their internal analysis that suggested that patients should have their blood levels monitored. A British Medical Journal investigation found that Boehringer Ingelheim did not release the analysis because it did not fit in with its marketing strategy.[8] Pradaxa had been heavily marketed as a drug that did not require patients to monitor blood levels, as opposed to the market leading anti-coagulant Warfarin.

Pradaxa has been 'associated with 280 deaths in Australia and 1,400 adverse drug reactions in the past five years, including abdominal bleeding, brain haemorrhages, strokes and heart attacks.'[9] This compared to Warfarin which has been linked 'to 30 deaths and 270 reactions over the same period.'[10] The drug company disputes that they ever withheld relevant data from regulators despite the fact that they are paying out $650 million to settle 4,000 lawsuits across the United States, evidence of the lack of disclosure of the drug's risks.[11]

More detail regarding Boehringer Ingelheim's failure to disclose Pradaxa's risks

Boehringer Ingelheim's internal research by one of its own clinical program directors, Dr Paul A. Reilly, had shown that there was an 'optimal plasma concentration' which could be attained through blood monitoring and which would be beneficial for some patients.[1] An internal email from a company supervisor stated that she could not believe that this research might be published by the company, an act that would undermine a decade's worth of work. She further added that it would be 'extremely difficult' to defend to the regulating authorities the company's claim that blood monitoring was not needed. 'I would like to ask you to check again whether this is really wanted,' she wrote about publishing the research.[2] Another internal email by yet another

[1] A federal judge in Illinois, overseeing a court case concerning whether consumers were warned by the manufacturer of Pradaxa about the risks, released internal emails, memos and internal presentations which related to whether an upcoming research paper would impact on the main selling point of Pradaxa. Katie Thomas, 'Study of Drug for Blood Clots Caused a Stir, Records Show', *New York Times*, 5 February 2014. Available at http://www.nytimes.com/2014/02/06/business/study-of-blood-clot-drug-pradaxa-unnerved-its-maker-documents-suggest.html

[2] Thomas, 'Study of Drug for Blood Clots Caused a Stir'.

company official stated that 'the publication [of the article] will [do] more harm than be useful for us…but especially harmful in the discussions with regulatory bodies.'[3]

When the research paper by Dr Reilly was published in the Journal of the American College of Cardiology, the research indicating that there was an optimal blood-level range had been omitted.[4] This information only came to light when an Illinois judge who is overseeing thousands of lawsuits lodged by people who claim that Boehringer Ingleheim did not properly warn them about the risks of taking Pradaxa.[5]

Enormous fines and settlement payments like that for Pradaxa seem to be accepted as just part of the cost of doing business for many of the world's largest pharmaceutical companies. From 2004 to 2013 in the USA, at least $19.47 billion in fines and settlements were paid for off-label promotion and marketing and fraudulent misbranding and marketing.[12] Companies fined include Johnson & Johnson, GlaxoSmithKline, Abbott, Novartis, Forest, AstraZeneca, Pfizer, Eli Lilly, Bristol-Myers Squibb, and Purdue.

For instance, in 2009 Eli Lilly paid $1.415 billion in fines and settlements for the 'off-label' promotion of Zyprexa for conditions such as dementia, agitation, aggression, hostility, depression, and generalized sleep disorder.[13] This is despite Zyprexa being an antipsychotic medication for the treatment of schizophrenia and bipolar disorder. In fact, Eli Lilly's own Product Information sheet carries a black box warning that 'Zyprexa is not approved for the treatment of patients with dementia-related psychosis' yet Eli Lily were fined for the off-label promotion for its use with dementia patients.[14] Many of the drugs which companies were fined for off-label promotion are mental health medications.

Strattera (atomoxetine hydrochloride) in Australia - Eli Lily have exhibited questionable behaviour in Australia when marketing as 'milder' their Attention Deficit Hyperactivity Disorder (ADHD) drug Strattera. [15] Strattera is Eli Lilly's brand name for atomoxetine hydrochloride, a noradrenaline re-uptake inhibitor. Strattera's legitimate marketing edge is that unlike dexamphetamine and Ritalin, it is not amphetamine based and has the advantage of being non-addictive and unsuitable for illicit use. Strattera was approved for sale in Australia in early 2004. It was licensed by the TGA on the back of evidence from two studies chosen by Eli Lilly.[16] Elli Lilly chose who conducted the studies and had the opportunity to present only those studies that supported its licensing application.[17]

When it came onto the Australian market it was promoted as a safer, milder alternative to ADHD amphetamines. Within two years it had the highest possible 'boxed' warning for suicidal ideation and a string of horrific adverse event reports for self-harm and suicidal and homicidal ideation by children as well as a warning for potentially fatal liver damage.[18] In 2012 a warning for *'clinically significant increases in heart rate and blood pressure'* was added.

On 1 October 2013, the TGA restated Strattera's suicidality warning and advised that a nine year old boy on Strattera had 'completed' a suicide and other children had made suicide attempts."[19] The real number of children who have suffered horrific side effects on Strattera will never be known as reporting is voluntary and only a tiny fraction of the real number are reported to the TGA.[20]

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3 Scott and Branley, 'Makers of blood-thinning drug Pradaxa'.

4 Paul A. Reilly, et al, 'The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)', *Journal of the American College of Cardiology*, Vol. 63, Issue 4, (2014), pp. 321-328

5 Thomas, 'Study of Drug for Blood Clots Caused a Stir'.

How this drug was originally licensed or approved for subsidisation, to the extent of $101.2 M over 4 years, through the Pharmaceutical Benefits Scheme will probably never be known. Commonwealth legislation exempts from Freedom of Information requests the documents used by drug manufacturer Eli Lilly to support their applications.[21] Eli Lilly's documents are given the same status as individual patient's medical records. The net effect is Eli Lilly get benefits from taxpayer subsidisation, at least one child has died, others have attempted to kill themselves, and the public are not allowed to know the details of why this drug was approved for market or PBS subsidisation.

Researcher financial ties to the pharmaceutical industry - Other Australian evidence of the problematic links between researchers and pharmaceutical companies was provided by a 2005 survey investigating the relationship between medical specialists and the pharmaceutical industry. 2,120 Australian specialists were approached for the survey and 39% (823) responded.[22]

The results showed that of greatest concern to respondents were 'instances of delayed publication or non-publication of key negative findings (reported by 6.7% and 5.1% of respondents, respectively), and concealment of results (2.2%). Overall, 71 respondents (8.6%) had experienced at least one event that could represent breaches of research integrity.' One hundred and ninety-six respondents (24%) reported 374 potentially undesirable outcomes of their research collaboration, including premature termination of trials, initial drafts written by company staff, delays in publishing results, and the failure to publish the key research findings from industry-sponsored research studies.

Other problems were cited such as report editing to enhance a drug's performance, being discouraged from 'presenting adverse reaction data from an unpublished study', and that it was 'common for adverse event data to be favourably analysed and selectively reported.[23] All up, the article reported that 143 incidents from 71 (8.6%) respondents were potentially serious breaches of research integrity.[24] Of course these results only reflected the responses of those who chose to participate and it seems likely that those who did not participate may be more likely to engage in questionable practices.

International Experience- In a similar vein an article in the *European Journal of Clinical Investigation* by Australian, British and US researchers has found that drug companies "masterfully influenced" medicine.[25] The researchers noted that the amount of profit in the manufacture and sale of drugs gave the industry 'power to influence every stage of the health system'. The report found that 'The benefits of drugs and other products are often exaggerated and their potential harms are downplayed'.[26]

In 2012 Canadian researcher Professor Marc-André Gagnon concluded that the 'dominant business model' of the pharmaceutical sector is to promote drugs that often don't offer any significant 'therapeutic advance'. He contends research is conducted by the pharmaceutical industry 'like a promotional campaign'.[27]

> Data obtained from clinical research are primarily used to boost and support sales rather than to improve prescribing behaviour… Ghost-writers are employed to inflate the number of publications showing the drug in a positive light; results that would harm sales are not published (publication bias); and negative data are suppressed… Pharmaceutical companies consider that private-sector clinical research produces private, confidential results that are their own intellectual property… And they are not compelled by political and health authorities to make public the data obtained in clinical trials.[28]

As evidence of these assertions Gagnon highlighted that:

> 'The [world's] 15 biggest drug companies… spend about twice as much on promotion as on research.'[29] 'In 2009, Prescrire analysed 109 new [to the French market] drugs or indications (excluding generics): 3 were considered a minor therapeutic breakthrough, 76 added nothing new to the existing pharmacopoeia, while 19 were deemed to represent a possible public health risk.'[30]

Gagnon's criticisms are largely based on his experience of the French and Canadian systems but are similar to those of critics of the USA drug licencing system administered by the Food and Drug Administration (FDA). Gagnon concluded 'as long as pharmaceutical companies hold the purse strings of biomedical research, medical knowledge will be selectively constructed for the purpose of marketing drugs rather than improving public health.'[31]

In the USA, pharmaceutical companies are free to determine who conducts their studies, which studies they publish and which they keep private. Some pharmaceutical companies use two methods to deny the FDA and the American public full information. The first is to ignore unfavourable studies. The second is to spin the results of unfavourable findings for the 'primary outcome' – the main question the study was designed to answer – and highlight a favourable 'secondary outcome'.[32] Pfizer, the manufacturer of antidepressant Zoloft, conducted five studies for presentation to the FDA in support of its application to licence Zoloft:

> The drug seemed to work better than the placebo in two of them. In three other trials, the placebo did just as well at reducing indications of depression. Only the two favourable trials were published, researchers found, and Pfizer discusses only the positive results in Zoloft's literature for doctors.[33]

These tactics are not limited to Pfizer. In 2008 the Wall Street Journal highlighted that in the case of 74 pharmaceutical company sponsored studies into antidepressants, 37 of 38 favourable studies were published, but the majority of unfavourable (22 of 36) studies were not. Of the fourteen unfavourable studies that were published, 'at least 11 of those studies mischaracterized the results and presented a negative study as positive… In nine (of 11) of the negative studies that were published, the authors simply omitted any mention of the (negative) primary outcome.'[34] There has been a sustained campaign by a number of US politicians, most notably Iowan Republican Senator Chuck Grassley to diminish the influence of the pharmaceutical industry. Senator Grassley had been involved in exposing unreported relationships between pharmaceutical companies and medical professionals. One example he exposed was where the Chairman of Psychiatry at Stanford University received a drug research grant whilst owning millions of dollars of stock in the company seeking federal approval for the same drug.[35]

Australian political inaction on Big Pharma influence - In contrast there has been little effort by Australian politicians of any persuasion to challenge the influence of the pharmaceutical industry. Rather, successive Commonwealth Governments have supported the pharmaceutical industry in the questionable belief that it would deliver significant benefit to the economy via research and manufacturing,

Has Australian Government support of the Pharmaceutical Industry delivered promised economic benefits?

Since 1988, there have been three programs set up by Australian governments to assist the growth of the pharmaceuticals industry. These were:

- The Factor f scheme (1988-1999) that provided nearly $1 billion to enable companies to further their Research and Development, manufacturing arm and export activity.
- The Pharmaceutical Industry Investment Program (the PIIP) (1999-2004) which was funding for companies to also further their R&D and production activities.
- The Pharmaceuticals Partnerships Program (2004-2009) to encourage companies to partner with Australian researchers.[36]

The influence of the pharmaceutical companies became even more entrenched in Australia after Prime Minister John Howard signed a Free Trade Agreement (FTA) with the USA in 2004. Medicines Australia on behalf of the pharmaceutical industry claimed the FTA guaranteed 'a more certain and fair business climate in Australia…more investment will be attracted, jobs will be created and exports increased. Our talented scientists will remain in Australia'.[37] At the time the Productivity Commission considered that the pharmaceutical industry was 'an icon of new economy manufacturing.'[38]

These optimistic predictions have not matched reality. When evaluated, these initiatives have received mixed findings as to their effectiveness. For instance, the Industry Commission in 1996 evaluated The Factor f scheme and found that 'companies were overcompensated for the levels of activity due to a too-high payment rate, and that the benefits generated did not outweigh the costs of the program or enhance the welfare of the community.'[39]

In 2007 the Centre for Strategic Economic Studies published a working paper in 2007 which noted that 'A significant part of the supply of pharmaceuticals in Australia is sourced overseas'.[40] Furthermore research and development undertaken by Australian companies is mostly 'clinical trials, involving specialist clinical research organisations',[41] and not manufacturing. More recently figures from 2009 show that the manufacturing of pharmaceuticals 'accounts for approximately 1% of Australia's total manufacturing workforce'.[42]

Global companies dominate the supply of pharmaceuticals in Australia, 'the 6 largest accounting for 50.5% of the market while the top 20 are responsible for 85.8%. Three Australian manufacturers – CSL, Mayne Pharma and Sigma – have a 4.8% share.'[43] There are still some drug manufacturing sites in Australia, for example Roche Products in Dee Why, NSW and Bristol-Myers Squibb Australia in Noble Park, Victoria, but in the twenty years between 1983 and 2002, local manufacture has decreased from being predominantly local to being dominated by brought-in ingredients.[44]

A 2014 report confirms these low manufacturing rates in Australia by noting that the small number of global pharmaceutical groups who dominate the Australian market, 'are engaged in 'actives

manufacturing' (i.e. active pharmaceutical ingredients). An increasing number of firms are limiting their Australian involvement to the later stages of the manufacturing process, such as dispensing, packaging and the fill-and-finish stage. Worse still a large number of players also restrict their Australian activities to distribution.[45]

Even *Medicines Australia* acknowledge that only a small number of pharmaceutical companies manufacture active ingredients, the remainder either manufacture only from the 'formulation stage through to packaging stage or undertake the fill/finish stage.' [46] Nonetheless *Medicines Australia* continues to trumpet the need for further government support, arguing 'If we can get the public and private sectors working better together, there's no reason what are currently small research labs couldn't grow into big exporters. It's a tough road but there are some real opportunities.'[47]

British House of Commons Inquiry - Whilst Australian politicians have shown little interest in tackling the influence of 'Big Pharma' there has been much greater recognition of the problem in other countries. In 2004-5 in response to concerns about the impact of inappropriate pharmaceutical industry influence on medical and psychiatric practice the United Kingdom House of Commons established a Committee to conduct an inquiry titled *The Influence of the Pharmaceutical Industry Fourth Report of Session 2004–05.*[48]
The Committee concluded that:

- 'Our over-riding concerns are about the volume, extent and intensity of the industry's influence, not only on clinical medicine and research but also on patients, regulators, the media, civil servants and politicians…
- The regulatory system, the medical profession and Government have all failed to ensure that industry's activities are more clearly allied to the interests of patients and the National Health Service.
- The influence of the pharmaceutical industry is such that it dominates clinical practice, to an extent that deprives it of independent and constructively critical feedback; this is a discipline it needs and which can help it to improve.
- The traditional secrecy in the drug regulatory process has insulated regulators from the feedback that would otherwise check, test and stimulate their policies and performance.
- The closeness that has developed between regulators and companies has deprived the industry of rigorous quality control and audit.
- Other bodies are in a position to provide feedback and quality control. They include academic, research, clinical and professional institutions, as well as the media and patient groups. However, representatives of these interests have had only limited success in containing excessive industry influence. This can be partly attributed to lack of transparency, limited resources, significant dependency on industry funding, and some conflicts of interest.'[49]

The report detailed 'problems with SSRIs antidepressants, notably Seroxat, and the COX-2 inhibitors, Vioxx and Celebrex'. It found unethical behaviour by drug manufacturers in failing to disclose adverse information when applying to licence new drugs. However, it also found that 'prescribers must take their share of the blame for the problems that have resulted' as some 'medicines have been indiscriminately prescribed on a grand scale'. It attributed this reckless prescribing to 'intensive promotional activity' and 'data secrecy and uncritical acceptance of drug company views'.[50]

The Committee concluded that the consequences of the above-mentioned failings were the 'unsafe use of drugs' and 'increasing medicalization of society'. They also found that the 'drift towards medicalization is a global phenomenon', and despite the problems identified above the 'UK may have

a better record than many others [countries]'. The Committee made a number of specific recommendations to tackle what it termed a 'pill for every ill' culture 'compounded by an excessive reliance on results from premarketing clinical trials, together with a failing system of pharmacovigilance'.[51] Given the cultural and institutional similarities between Australia and the United Kingdom, the House of Commons Committee's conclusions and recommendations may have relevance in Australia.

The committees' recommendations included:

- A 'clinical trials register be maintained by an independent body and the results of all clinical trials data, containing full trials information, be put on the register at launch as a condition of the marketing licence'.
- Limitations on, and health regulator's approval of, promotional materials sent to and promotional visits to potential prescribers.
- 'When companies are found to be in breach of advertising regulations or to have published misleading findings, the allowance for promotion and research, respectively, provided under the [National Health] Scheme should be reduced'.
- Full public disclosure of information used by pharmaceutical companies to apply to license and otherwise regulate drugs.
- Systemic random audits of raw data used in research supporting licensing etc.
- Greater follow up of adverse reactions within research trials that prevented ongoing participation.
- Establishing five year post market surveillance of the safety and efficacy of newly licenced medicines.
- Improved post marketing reporting of adverse events by healthcare professionals.
- Restrictions on what professions can prescribe new medications for two years post licensing (for example only psychiatrists to prescribe new psychotropic medications)
- A 'public inquiry whenever a drug is withdrawn on health grounds' in order to prevent similar occurrences.
- Improved training of medical students on 'how to judge clinical trial results effectively, recognise adverse drug reactions and deal with drug company representatives'.
- 'Mandatory post-graduate training for all prescribers to keep up-to-date with prescribing changes'.
- 'Stricter regulation of individual prescriber's practices'.
- Establishment of a publicly available 'register of interests' of 'all substantial gifts, hospitality and honoraria' received by prescribers and researchers.
- Public disclosure of industry sponsorship of 'disease awareness campaigns' and 'patient [support] groups.[52]

Summary - Australian and international experience demonstrate that the enormous economic incentives and resources, and political and marketing skills of the pharmaceutical industry make preventing the 'regulatory capture' of pharmaceutical licencing and subsidisation processes a challenging process. However, the potential savings, both financial and in terms of avoiding 'iatrogenic harm' (including deaths) are considerable. It is essential that regulatory processes are both transparent and effective. The following seven reforms are designed to achieve this.

Seven Transparency Reforms on Pharmaceutical Regulation

Transparency Reform 1 - FREEDOM OF INFORMATION REFORM

Reform Commonwealth Freedom of Information legislation to end the entitlement of corporations to rely on privacy provisions originally intended to protect the health records of individuals.

Section 135A of the *Health Act (1953)* prevents anyone working for the Commonwealth Government revealing information relating to the affairs of a (legal) person. Specifically it states:

> (1) **A person shall not,** directly or indirectly, except in the performance of duties, or in the exercise of powers or functions, under this Act or for the purpose of enabling a person to perform functions under the Medicare Australia Act 1973 or the medical indemnity legislation, and while the person is, or after the person ceases to be, an officer, **divulge or communicate to any person, any information with respect to the affairs of a third person** acquired by the first-mentioned person in the performance of duties, or in the exercise of powers or functions, under this Act.
> Penalty: $5,000 or imprisonment for 2 years, or both.[53]

In November 2008 I (Martin Whitely) requested, via Freedom of Information, copies of all documents relating to the decision of the Pharmaceutical Benefits Advisory Committee (PBAC) to recommend ADHD drug Strattera's (manufactured by Eli Lilly) listing on the PBS.[54] I was particularly interested in what consideration had been given by the PBAC to Strattera's (highest possible) boxed warning for suicidal ideation and the numerous serious adverse event reports.[55] The Department of Health and Ageing (DoHA) refused to release all but a tiny percentage of heavily redacted and irrelevant documents.

In April 2010 the Administrative Appeals Tribunal (the Tribunal) heard my appeal against DoHA's refusal to release all the documents.[56] The DoHA lawyers argued successfully that they had erred in giving me any documents because, for the purposes of the abovementioned provision, Eli Lilly was a 'person' entitled to privacy protections. This sixty year old provision appropriately protects the privacy of patients, however the 2010 decision by the Tribunal established that the same privacy protections extend to the affairs of corporations. My argument to the Tribunal that it was in the 'public interest' to know what safety and efficacy data the PBAC had considered before recommending that Strattera be placed on the PBS was considered irrelevant. The privacy provision of the *Health Act (1953)* trumped any consideration of the 'public interest' in the *Freedom of Information Act 1982*.

Section 135A of the *Health Act (1953)* is one of more than 65 secrecy provisions from over 28 Acts and one sub-regulation listed in schedule 3 of the *Freedom of Information Act* that are exempt from FOI requests.[57] [58] There are sound reasons for secrecy provisions in regards to personal information and issues of national security. However, Section 135A denies the public the right to know why the PBAC recommends taxpayers subsidising any drug. It also exempts all interactions of the Health Department and commercial operations from scrutiny via FOI processes. This means that the operations of the TGA are similarly exempt.

In 2010 the the Australian Law Reform Commission (ALRC) produced a report titled *Secrecy Laws and Open Government in Australia*.[59] The ALRC recommended a wholesale review of secrecy provisions in commonwealth legislation. It stated secrecy provisions should only remain 'where they are necessary

and proportionate to the protection of essential public interests of sufficient importance to justify criminal sanctions'.[60]

In the case of Strattera, Eli Lilly benefited from a taxpayer funded price subsidy (worth an estimated $101.2 million over four years) for a drug that is known to increase the risks of suicidality, potentially fatal liver problems and heart attacks and strokes.[61] For drugs like Strattera it is in the public interest to know whether taxes are being well spent and if government agencies responsible for enhancing patient wellbeing are considering relevant safety and efficacy evidence. The 'protection of essential public interests' requires disclosure not secrecy.

Note: This reform is a necessary pre-requisite for the following reform.

Transparency Reform 2 - PUBLIC DISCLOSURE OF EVIDENCE USED FOR TGA AND PBS DECISIONS

Require full public disclosure of all relevant safety and efficacy data (with protections for intellectual property and commercially sensitive information) of all evidence regarding pharmaceutical products approved for market and/or subsidised for use in Australia.

Details of all research conducted on drugs approved by the TGA and those subsidised by the PBS should be provided to the relevant regulator for consideration and made available for public scrutiny. This would help to address the problem of a narrow base of selective research used to licence and subsidise drugs. Regulators would have access to all related research. The public, including interested researchers and the media, would also have the opportunity to properly scrutinise PBS and TGA decisions and ensure the rigour of licencing and subsidisation processes.

Transparency Reform 3 - PRE-REGISTRATION OF PHARMACEUTICAL COMPANY RESEARCH

Prevent 'cherry picking' of favourable results by requiring pre-registration of all new research that may be later used to support the TGA licencing and PBS subsidisation of pharmaceutical products in Australia.

In 2003 the TGA and the National Health and Medical Research Council (NHMRC) commissioned a 'Review of the Australian arrangements for clinic trials and access to unapproved therapeutic goods' (The Review).[62] The Review also investigated barriers to clinical research and also the possibility of establishing of a clinical trials register. The Consumers Health Forum, the national peak body representing the interests of Australian healthcare consumers, had previously argued that a register would provide increased and up-to-date access to information about trials. A register would also detail follow up findings, including negative or adverse findings.[63]

The Review appears to have been heavily influenced by pharmaceutical company concerns. It noted that while several stakeholder groups wanted a clinical trial register, they did not agree on the scope of the register and what information should be provided. The Review found that 'the expectations from a register were somewhat unrealistic'.[64] While acknowledging that there 'were valid arguments that a register may address issues of negative publication bias in scientific journals and prevent repetition of research, and thus wasting of resources', it was concluded that a review could not be implemented until clear decisions were made on what a register would look like and what it needed to achieve.[65]

Pharmaceutical industry stakeholders argued that the level of information that would be entered on the register would impact on their 'commercial confidentiality'.[66] The Review also noted that if a mandatory register was implemented it might be a path to ensuring 'cutting-edge clinical research is

carried out in other countries', resulting in delayed access to therapies for the Australian public.[67] The review did recommend that a register should be set up which would list all clinical trials, with enough detail to provide information on ongoing or completed trials so that interested parties could contact trial sponsors to inquire about the outcome of the trials.

A clinical trials register was set up in 2005, the Australian New Zealand Clinical Trials Registry (ANZCTR). The ANZCTR is a Primary Registry in the World Health Organisation (WHO) Registry Network. Trials are registered from all countries and include trials involving pharmaceuticals, surgical procedures, complementary therapies, and preventive measures.[68] However, registering clinical trials on this site is not mandatory, and it is up to the sponsor of each trial to provide accurate data. All that is required if a trial is registered are its objectives, main design features, sample size and recruitment status, treatments under investigation, outcomes being assessed, principal investigators, and contact details for specific trial information.[69] This is inadequate to prevent cherry picking by pharmaceutical companies of research used to support licensing and subsidisation applications.

A mandatory public registration of research (regardless of where it is conducted) that may be relied upon later by pharmaceutical companies applying for TGA licencing or PBS subsidisation will help stop cherry picking. The purpose of the research and proposed methodology could be recorded in advance. The results of the research in terms of safety and efficacy could be recorded after the research is completed. This system would help prevent pharmaceutical companies hiding negative results or adjusting the purpose or methodology of research 'post hoc'.

The HCC recognises it is unreasonable to expect pharmaceutical companies to expend significant resources developing new products and then relinquish control over the conduct of their research. The situation is further complicated by the globalised nature of pharmaceutical research as it would be impractical and wasteful to require national licencing and subsidisation of pharmaceutical products purely on intra-national research. A system that rewards pharmaceutical companies for transparency and innovation and invention by protecting legitimate 'commercial in confidence information' – such as chemical formulations and financial information - but prevents the selective disclosure of safety and efficacy data is required.

Obviously this system would only work prospectively and not enable access to studies already concluded. The reforms proposed above at 1 and 2 will help deal with the issue of disclosure of existing research.

The International push for an AllTrials Register

Ben Goldacre, author of *Bad Pharma: How drug companies mislead doctors and harm patients*, is the founder of the AllTrials campaign, which is a global online campaign calling for full clinical study reports, on all current treatments, to be published. A petition stating 'All trials past and present should be registered, and the full methods and the results reported' has been signed by approximately 80,000 people and 501 organisations.[70] Information on the campaign website notes that around half of all clinical trials have never been published, and trials with adverse findings are also generally not published. An example is provided whereby Roche, the manufacturer of Tamiflu, and on which the UK government spent £500 million in 2009 alone, published less than half of the trials conducted and continues to stonewall doctors and researchers regarding trial information.[71] In the US, clinical trial results since 2008 are required to be published within a year of the trial being completed. However, in a 2012 audit, figures show that 80% of trials did not comply with this law.[72]

Transparency Reform 4 - ADEQUATE DISCLOSURE OF RISKS TO CONSUMERS IN AND ON PHARMECEUTICAL PACKAGING

Strengthen Consumer Medicine Information (CMI) requirements so that

- **Every warning currently included in information to prescribers is also on the CMI**
- **It should also be mandatory to include a CMI inside a medications packaging.**
- **Putting a brief summary of the most serious (boxed) warnings on the outside packaging of drugs so consumers are aware of very significant risks.**

Currently boxed warnings are often only highlighted on information made available to prescribers and are not seen by consumers.

A Product Information sheet provides health professionals with the scientific information they require to safely and effectively dispense prescription or pharmacist-only medications. The information is supplied by the drug manufacturer and covers a range of information including pharmacology, contraindications adverse effects, clinical trials and the poison schedule of the medicine.[73] Where there are severe risks Product Information sheets will have a 'boxed warning', the strongest form of warning issued by the TGA.

Product information sheets are rarely given to consumers, but consumers can ask their doctor or pharmacist for a copy if they know that they exist. Instead they may receive Consumer Medicines Information leaflets (CMIs). TGA regulations require that the CMI is available to consumers on request, 'either in the pack or in another manner that will enable the information to be given to the person to whom the medicines are administered or otherwise dispensed'.[74] In other words consumers do not automatically receive a CMI. They will only get one if the prescribing doctor or dispensing pharmacist gives them one; or if the manufacturer includes a CMI inside the pill box; or if they ask for one.

CMIs contain some information regarding the safe and effective use of a prescription or pharmacist-only medicine. The information in a CMI is provided by the drug company that developed the medication. The format of the CMI is set out in the Therapeutic Goods Regulation in Schedule 12. Information provided in a CMI includes names of the ingredients, dosage, side effects, how to use the medicine properly, and warnings and precautions such as when to take the medicine. However, unlike the Product Information sheet, CMIs do not need to carry a black box warning in the same format. The warning is required on the CMI, and must be consistent with the boxed warning on the Product Information sheet, but the wording can be different because of a different audience, and often it is not in a format which makes it clearly stand out to consumers.

Despite there being no standard requirement for the CMI to have the boxed warning in a text box, the TGA can request this at the time when the boxed warning is imposed on the PI. It is up to the drug companies whether they comply or not. Commendably some pharmaceutical companies portray the boxed warning information prominently. For example Aspen Pharmacare Australia have provided a bolded and boxed warning on the front page of the CMI for Doloxene (dextropropoxyphene napsylate), a pain relief medication which can be fatal even with a small overdose.[75] Another example of a prominent warning is for the drug Stilnox (zolpidem tartrate), a drug for insomnia. Although the warning is not in a box, it is bolded and at the top of the CMI. [76]

On the other hand Eli Lilly's Strattera CMI leaflet does not highlight an obvious warning for the risk of suicidality, despite the issue of a boxed warning in 2006.

The boxed warning required on the Prescribing Information states;[77]

Strattera increases the risk of suicidal thinking in children and adolescents with ADHD. Patients who are started on therapy should be observed closely for clinical worsening, suicidal thinking or behaviours, or unusual changes in behaviour. Families and caregivers should be advised to closely observe the patient and to communicate changes or concerning behaviours with the prescriber.

The CMI for Strattera, however, only mentions thoughts or talk of suicide amongst all other signs listed to watch for, including insomnia, irritability, and anxiety.[78] There is no obvious warning on the CMI to alert consumers to the risks, despite the numerous adverse events reported. [79] Companies like Eli Lily should not benefit by being 'less than forthcoming' about safety and efficacy data. Consumers must have easy access to information concerning drugs they are being prescribed. Strengthening CMI requirements to properly reflect issued warnings would assist consumers in making informed decisions.

Transparency Reform 5 - MANDATORY REPORTING OF SEVERE ADVERSE EVENTS

Make adverse drug event reporting to the TGA for a specified range of serious reactions (suicidal ideation, strokes, psychosis etc.) mandatory and regularly publish full de-identified details on the TGA website.

Voluntary reporting means that only a tiny fraction of adverse events ever get reported. A 2008 study by Curtin University pharmacologist Con Berbatis identified that for the prescription of all drugs by Australian General Practitioners only two percent of adverse events are reported.[80] In 2013, the TGA reported that of the 14,500 adverse event reports it received, general practitioners (GPs) were responsible for only 5 per cent, down from 7 per cent in 2011.[81] Currently, the Royal Australasian College of Physicians (RACP) acknowledge that nine per cent of healthcare practitioners reported adverse events to the TGA.[82] Although these figures vary, they all indicate non-reporting of adverse events is the norm. Arguably clinicians who prescribe recklessly may be less likely to report serious adverse events than cautious prescribers as they may be concerned about the consequences of acknowledging their prescribing practices.

The Royal Australasian College of Physicians (RACP) advocates mandatory reporting as submitted in their 2013-14 budget submission papers. The RACP argues that the economic cost of an adverse event to the Australian public is considerable as the consequences can be extra visits to both GPs and hospitals.[83] The RACP also advocates remuneration for healthcare practitioners for time spent in reporting and utilising 'personally controlled electronic health records as an additional means of ensuring more timely detection of drug-safety problems.'[84]

In 2004, the Australian Health Ministers mandated that all public hospitals were required to have an incident reporting system by January 2005, however not all incidents required mandatory reporting.[85] In New South Wales hospitals all clinical incidents are required to be reported,[86] however in Western Australia mandatory reporting is only required when there is an incident that resulted in either death, very serious harm, or a near miss.[87] In Victoria, all clinical incidents denoted severe or which result in death must be reported and reviewed by health services, lesser incidents are reported but handled internally.[88]

Building on this to mandate reporting of serious adverse events by prescribers, health professionals and pharmaceutical companies to the TGA would help build a more accurate risk profile of medication. The TGA should then publish this data as the public has a right to know about the frequency of adverse events. Similarly policy makers need to know so they can make informed decisions when subsidising, licencing, placing warnings on or removing from market, medications.

Transparency Reform 6 - DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Require full public disclosure of pharmaceutical industry funding sources for clinicians, researchers, patient groups, advisory board members and members of committees involved in regulatory and policy development processes.

United States Senators Chuck Grassley, (see page 7) and Herb Kohl co-authored a bipartisan Physician Payments Sunshine Act which was enacted in March 2010. The Physician Payments Sunshine Act required manufacturers of drugs, devices, biological, or medical supplies to report payments or transfers of value provided to doctors and teaching hospitals, to report shareholdings, and for this information to be published annually on a public website, by physician name.[89]

In Australia *Medicines Australia* responded to calls for the adoption of legislation similar to the Physician Payments Sunshine Act by establishing the Transparency Working Group (TWG) in August 2012. The TWG was set up to develop 'a model for introducing greater transparency relating to payments and transfers of value between companies and healthcare professionals.'[90] The TWG produced a discussion paper for consultation and discussion and included in the paper were suggested exclusions from reporting requirements. These included such items as:

- Any payment associated with clinical research
- A dividend or other profit distribution arising from personal ownership or investment interest in a pharmaceutical company security or mutual fund instrument
- Travel and accommodation expenses for attending Continuing Professional Development (CDP) activities
- Payments or other transfers of value greater than $25 provided at large-scale conferences and similar large-scale events
- Starter packs for patient use
- Payments to healthcare professionals acting as expert witnesses in legal or administrative proceedings.

The discussion paper appeared to promote transparency about payments between drug companies and some health professionals. However the proposed system will allow clinicians, researchers and other parties to opt out from disclosure and public reporting requirements. A voluntary system will achieve nothing except to create a false impression to casual observers that transparency has been achieved.

Compulsory disclosure like that mandated in the Sunshine Act is required. Parents and patients are entitled to know what factors other than patient welfare might be motivating the doctors and patient support groups that are advising them. Likewise, government and the public are entitled to know about the commercial ties of researchers and advisers.

Transparency Reform 7 - BRINGING "OFF LABEL" PRESCRIBING "ON LABEL"

The Commonwealth Government should commission or conduct research into the incidence and impact of 'off label' prescribing. The research should concentrate on the health impacts of off label prescribing and the extent of PBS subsidisation of the off label use of medications. Based on the outcome of this research the Commonwealth Government may consider if over time it is worth encouraging 'off label' prescribing to become 'on label'. This could be achieved by gradually enforcing PBS subsidisation of medications to those prescribed within the approved guidelines. This may encourage pharmaceutical companies to apply to the TGA to expand the range of authorised uses of their products and would help ensure that prescribing practices are supported by robust evidence.

Pharmaceutical companies receive approvals from the Therapeutic Goods Administration (TGA) to market drugs for the treatment of conditions within specified guidelines. However once a drug has been approved doctors are free to prescribe it as they see fit, even in contravention to the manufacturer's recommendations ('off label' use). 'Off label' prescribing occurs so regularly that it has, in many cases, become the norm. A 2009 study found that 62 percent of U.S. pediatric office visits included off label prescribing, with younger children at higher risk of receiving off-label prescriptions.[91] In 2003 an Australian nationwide survey of 435 general paediatricians and 187 child and adolescent psychiatrists 40 percent reported off-label prescribing of psychotropic medications.[92]

Off label prescribing does not necessarily result in adverse outcomes, often patients benefit. But it is unregulated and outside safety parameters established through licencing process. The extent to which medications that are listed on the PBS and prescribed 'off label' receive full subsidy is unknown but the cost is likely to be substantial. The net health benefit (or loss) of off label prescribing is also unknown and warrants investigation.

CONCLUSION

Despite a generally positive perception Australians, both as taxpayers and consumers, are not well served by our current system of subsidising and licencing pharmaceuticals. Successive governments have protected the pharmaceutical industry, providing too much in taxpayer funded support and requiring too little accountability. Promised jobs and economic benefits from a home grown pharmaceutical industry have failed to materialise. Worse still, inadequate safety and efficacy regulations have enabled the licencing and subsidisation of products that have, on occasions, caused significant harm including entirely avoidable deaths.

Urgent reform along the lines of those suggested in this paper are needed. Establishing rigorous and transparent processes for ensuring the safety and efficacy of medications should be a national priority.

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