

Responses to questions on notice: Dr Deborah Gleeson

1) Prospect of achieving reform through WIPO/WTO and other multilateral forums p.464

'Your submissions and your opening remarks also refer to the potential for Australia to pursue, through multilateral means of negotiation, any changes to intellectual property arrangements. Indeed, our draft report, perhaps a little optimistically so, suggested that it might be time for us to identify some like-minded countries who might be able to work with us to, over time, remove some of those policy flexibility constraints.

It would just be good to get your thoughts on, I guess, firstly, how realistic is it for us to expect that to happen, given developments with the WIPOs and WTOs of the world and then, secondly, what mechanism or what cluster of like-minded countries, or are there other ways that you think that we could achieve reforms over time, through multilateral means?'

Response:

The first thing to mention is that the TRIPS Agreement actually already allows significant policy flexibility around intellectual property (IP) settings. The main problem as I see it is that bilateral and plurilateral trade agreements negotiated over the last 20 years have progressively undermined that flexibility and bound countries to increasingly TRIPS+ levels of IP protection (see, for example, t'Hoen, 2016, Lopert & Gleeson, 2013; Sell, 2011). So to restore that policy flexibility would really require renegotiation of these prescriptive TRIPS+ agreements.

For Australia, the main problem is the Australia-US Free Trade Agreement (AUSFTA) – and the TPP, if ratified, will further entrench the TRIPS+ measures which are mandated by the AUSFTA. Renegotiation of AUSFTA to remove the requirements for secondary patenting, patent term extensions, data protection, and patent linkage should be a priority.

So I'm not convinced about the prospects for using multilateral forums like the WTO and WIPO to restore the policy flexibility that has been undermined by bilateral and plurilateral trade agreements. However, I think that Australia should support moves through the World Health Organization and other UN initiatives to de-link funding of research and development (R&D) from drug prices, including the binding international treaty on R&D funding that was proposed by the WHO Consultative Expert Working Group on R&D Financing and Coordination in 2012. It will also be important for the Australian Government to pay close attention to the findings of the UN High Level Panel on Access to Medicines (see <http://www.unsgaccessmeds.org/the-process/>) and consider how Australia can support any strategies recommended by the Panel.

It would be worth considering whether there might be opportunities in the longer term to use trade agreements to actually reinforce and support TRIPS flexibilities rather than undermine them. For example, we could use trade agreements to enforce high standards of patentability, or make compulsory licensing automatic when prices are above a certain threshold. Trade agreements could also be used to encourage support for international efforts to address policy incoherence between IP rights and access to medicines.

2) TRIPS review mechanism Article 71 p. 465

'We learned recently, when we were meeting with some folk in Geneva, that within TRIPS there is an unused or unutilised clause for a review of TRIPS and a little ambiguously worded, unsurprisingly, as to what the scope of that is meant to be and the regularity of it. But if TRIPS is our benchmark could

one mechanism be reviewing whether or not that benchmark has remained enduring as an appropriate benchmark for getting the balancing act of intellectual property arrangements right globally?’

Response:

I am not very optimistic that a review of TRIPS at the present time would be an effective strategy to remove barriers to affordable access to medicines. As I mentioned at the hearing, the global pharmaceutical industry is very powerful, and the United States and European Union, in which the bulk of the world’s transnational pharmaceutical companies are headquartered, tend to dominate the standard-setting process (Gleeson et al, forthcoming). This is compounded by the political influence of the industry in the US and the regulatory capture of the Office of the US Trade Representative by the pharmaceutical industry, as described by Margot Kaminski (2014). Peter Drahos has written extensively about the ‘webs of coercion’ the US and EU exert in these forums (see, for example, Drahos 2005).

The negotiation of the TRIPS Agreement was very fraught and contested and the resulting agreement was in many ways not in the interests of developing countries. Since the TRIPS Agreement, countries have come under a lot of pressure not to use the legal flexibilities permitted under TRIPS and affirmed in the Doha Declaration on the TRIPS Agreement and Public Health (see ‘t Hoen 2016 for a helpful account of these events). These same dynamics would be likely to come into play if TRIPS were re-opened, with the pharmaceutical industry (and the US and EU on its behalf) seeking interpretations of TRIPS that further limit developing countries’ prospects for compulsory licensing and freedom to design their patent laws in the interests of access to medicines.

However, discussions in forums outside of the WTO might help to build consensus towards focused reform of the TRIPS Agreement in ways that facilitate access to medicines. Re-opening the TRIPS Agreement without such a consensus could be counter-productive.

3) Delays in PBAC approval: regulatory delays vs delays the pharmaceutical company has control over (p. 466)

‘So I guess for us to step back then and understand that tension against pharmaceutical companies suggesting that there are delays through the PBAC process, given your understanding of the PBAC process, how much of that negotiation really is a commercial negotiation and that’s where the function of the timeline really rests? i.e. how much of it can be really influenced by the pharmaceutical company and how much of it is a regulator process that the pharmaceutical company really has no influence over?’

Response:

The assistance of Dr Ruth Lopert (George Washington University) and Dr Hazel Moir (Australian National University) in responding to this question is gratefully acknowledged.

Delays in the time between TGA approval and PBS listing can occur at multiple stages; these will be considered separately below.

a) Between TGA approval and submission of the first application to the PBAC

There is often a long delay between TGA approval and submission of the first application to the PBAC. A study by Pearce et al (2012) tracing the approval process timelines for new chemical entities and products for new indications approved by the TGA in 2004 found that an application was submitted to the PBAC within 2 years for only 43% of these products.

These delays are clearly the responsibility of the pharmaceutical companies. It should also be noted that companies can apply to PBAC before they obtain approval from the TGA, so there is no reason from a regulatory point of view for delays at this stage.

b) The PBAC process

The time taken for a PBAC decision on a certain application is fixed at 17 weeks. Pearce et al (2012, p. 413) found that the main reasons for a negative or deferred recommendation were “unacceptable cost effectiveness” or “uncertain clinical benefit”. There are several ways that companies can reduce the chances of a negative or deferred recommendation (Pearce et al, 2012). If a negative recommendation is made, an application is often resubmitted with a reduced price, narrowed population, or better evidence of benefit over the comparator. More careful consideration of these issues prior to the first submission would increase the chances of a positive recommendation. Delays between a negative recommendation and a resubmission while companies reconsider their price and collect further evidence are not the responsibility of the PBAC.

See the case study of panitumumab below for an example of how the actions of pharmaceutical companies are often responsible for long delays between TGA approval and a positive recommendation for PBS listing by the PBAC.

c) Time taken between a positive PBAC recommendation and PBS listing

This can be affected by a number of factors including the length of commercial negotiations and budgetary issues. Pearce et al found that delays earlier in the process were more significant, and many of these were due to the actions of the companies rather than the regulatory processes themselves.

Another issue that should be taken into account when considering industry arguments that they should be compensated for the time taken for PBAC approval and listing on the PBS is that PBS listing is not an absolute barrier to entry to the Australian market. Companies can still sell their products to hospitals and the private market regardless of the length of time taken for PBS listing.

Essentially, compensating companies with additional years of monopoly privileges for delays for which they are the main cause, and when they are still able to access the market in other ways, does not make good policy sense and would result in unnecessary costs without corresponding benefits to the Australian public.

It can also be argued that extending the term of a patent would be the wrong compensation for a delay in market entry, even if such a delay were due to regulatory inefficiency rather than inflated price demands and inadequate evidence presented by the pharmaceutical company. Stuhldreier (2016) points out that it is patients who bear the cost of patent term adjustments; a better alignment of incentives, if compensation were justified (and the evidence suggests it is not) would be a direct payment by the regulator in lieu of the profits lost during the period before market entry.

Case study: Panitumumab

There are myriad examples illustrating the role of pharmaceutical companies in delays in obtaining PBS listing. One such example is panitumumab (Vectibix). **Five** submissions were made to the PBAC between 2008 and 2015.

Panitumumab was registered by the TGA in May 2008 and in **November 2008** the PBAC considered the first submission by Amgen Australia Pty Ltd seeking second-line treatment of “K-RAS wild type (WT) metastatic colorectal cancer (mCRC), after failure of treatment with a fluoropyrimidine, irinotecan and oxaliplatin” (PBS, 2008). The PBAC rejected the application due to “**uncertainty about the extent of clinical benefit over best supportive care [the comparator]**, both in terms of progression free and overall survival, and because of the resultant **high and highly uncertain cost effectiveness ratio**” (PBS, 2008).

It was not until **more than four years later** (March 2013) that a second submission was made to the PBAC for panitumumab. The second submission sought PBS listing for two indications but for a subset of patients with K-RAS wild-type metastatic colorectal cancer (PBS, 2013a): i) as a second or later line treatment after failure of first-line chemotherapy; and ii) as a first line in patients for whom Avastin was “unsuitable”.

The outcome of the second submission was that PBAC **recommended listing panitumumab as a later-line therapy but rejected the application for first line treatment** “on the basis of inadequate clinical trial data to support listing for the intended patient population.” (PBS, 2013a). However the **recommendation was that panitumumab be listed on a cost minimisation basis**, with the price to be lower than the comparator cetuximab as there was insufficient evidence that panitumumab was not in fact inferior. **Amgen Australia Pty Ltd did not proceed with the listing** at this stage, but made a subsequent application to the PBAC in November 2013, which finally resulted in a recommendation for listing panitumumab “on a cost-minimisation basis compared with cetuximab” (PBS, 2013b).

In **July 2014**, the sponsor again unsuccessfully sought listing for **first-line** treatment; the PBAC rejected the application because of **uncertainty about the extent of incremental clinical benefit over the comparator** (PBS, 2014). Finally, a **fifth submission** to the PBAC resulted in a listing for first line treatment with panitumumab on a cost minimisation basis with cetuximab – reflecting a lack of evidence of incremental benefit over the comparator (PBS, 2015).

On the basis of the PBS public summary documents, the delays in this case appear to result from the sponsor taking more than four years to resubmit the application after the first submission, declining to proceed with the listing at a lower cost than cetuximab, and failing to recognise the limitations of the evidence presented or to moderate the price to achieve reasonable cost-effectiveness. These types of actions on the part of pharmaceutical companies should not be rewarded with a longer monopoly period.

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