Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists

Review of Medicines and Medical Devices Regulation Secretariat
Department of Health
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Review of Medicines and Medical Devices Regulation

Dear Review Panel,

The Clinical Section of ASCEPT led by Professors Gillian Shenfield, Jenny Martin (ASCEPT Council) and Dr Darren Roberts (Chair Clinical Pharmacology Special Interest Group) have coordinated a response to the Review of Medicines and medical Devices Regulation.

On behalf of ASCEPT I submit their response for consideration by your panel.

Yours sincerely,

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ASCEPT Response

Abstract

- Members of The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) have experience of all aspects of the TGA's regulation of Medicines.
- Overall we consider that the TGA performs extremely well compared with Respected overseas Regulators
- There are a number of examples in which the TGA has performed with more appropriate caution than most other Regulators eg dabigatran, metformin and currently e-cigarettes
- For prescription medicines we recommend that the TGA should not automatically follow overseas Regulators but perform its own assessments in the Australian context.
- For generic medicines overseas approvals could be accepted if the new product has demonstrated bioequivalence with the original product
- For new OTC products the Sponsor would need to provide evidence of bioequivalence and labelling in line with current Australian guidelines.

ASCEPT Response

The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) is the leading Society of Therapeutics in Australia and New Zealand. As its name suggests members include Clinicians, Academics, Research Pharmacologists and Chemists, Pharmacists and Toxicologists.

Since the inception of the Therapeutic Goods Authority (TGA), members of ASCEPT have worked closely with the TGA to ensure the safety, efficacy and quality of Australian medicines. Our members have been appointed to, and often chaired, each of the TGA Advisory Committees[1] (ADEC history). They have assessed medicines from chemical, pharmaceutical, clinical and toxicological aspects. Some ASCEPT members have performed bioequivalence studies for the TGA. Others have worked within the TGA and Industry, and have experience in overseas agencies who perform similar functions (including the US Federal Drugs Agency (FDA) and the European Medicines Agency (EMEA)).

Collectively, therefore, we have extensive experience of working with the TGA, critically comparing and contrasting TGA decisions with decisions from international bodies. We consider its works to be of a world-class standard and are concerned by moves that may threaten this.

Review of Medicines and Medical Devices

Our expertise relates to Medicines so we will not consider Devices in this submission. Also, given the very short time frame provided for submissions, we will not attempt to answer every question listed in the Review in detail, but will instead present an overview of the document. Please note the bold-text is our emphasis.

Chapter 3 Principles

We strongly support the five listed Principles on Page 3 of the Discussion paper.

1. The role of regulation is to **manage risk** in order to **protect public** health and **safety**.
2. The level of **regulation** should be **commensurate with the risk** posed by the regulated products.
3. A **risk-benefits approach** to the regulation of therapeutic goods **is appropriate**.
4. The **regulation** of therapeutic goods **should take a whole of lifecycle approach**.
5. Australia should **maintain** its **capacity to undertake assessments** of medicines and medical devices **for Safety, Quality and Efficacy.**

- ***We consider that these should be the foundations of all Medicines Evaluation and should never be sacrificed under pressure from external groups, including patient organisations or Industry.***
- ***The need for Australia to maintain its regulatory capacity is essential because of differences in climate, population and sometimes medical practices to those in other countries. This point is vital to understand as it recognises that Australians may respond to medications differently and be at risk of different side effects and drug interactions than patients in other countries.***

THEME 1 DUPLICATION OF REGULATORY PROCESSES

1. **Issue 1: How might a Trusted Overseas Regulator be Defined?**

We do not think the question can be answered in this form because ALL Regulators sometimes make mistakes and overestimate efficacy and/or safety[2/3]. In the case of metformin it took some regulators outside of Australia over 20 years to reach an appropriate position[4]. The MHRA, EMA and FDA have each made decisions that were subsequently noted to be erroneous. Indeed, the benefit of having three different review processes has meant that expertise can be pooled, as in the cases of lumiracoxib[5] and cerivastatin.

There are many reasons for errors in estimation of toxicity and efficacy. These are mostly attributed to the combination of (a) Industry requirements to make profits for their investors (appropriate for any business), and (b) patients wanting instant access to medicines in development stage, given perceptions that newer medicines are safer and/or more effective. These motivations may be legitimate, but they may also lead to fraud of omission by industry.

The new generation of anticoagulants is a very good example of such complexity. In the case of dabigatran, regulators were not given evidence showing that monitoring drug plasma concentrations could improve safety[4]. An in depth study using Freedom of Information laws has discovered that the manufacturer of dabigatran had taken blood samples to assay drug levels during the sentinel RE-LY trial without it being part of the protocol. [4] The results showed correlations of drug concentrations with both efficacy and toxicity (excessive bleeding). This information was not submitted to the regulators who, therefore, over-estimated efficacy and underestimated likelihood of bleeding. The net effect is inadequate therapy, or unnecessary complications and deaths, to Australian patients.

There are other examples where pressure from consumers, the media[6] and Pharma (using start-up/familiarisation packs) for new medicines to be registered in Australia before the safety data is mature has caused severe morbidity and death. Examples include celecoxib and rofecoxib (note New Zealand did wait until safety data were mature), mibefradil, gabapentin (trials subsequently showed Pharma fraud) and selected glitazones. Nasty deaths and morbidity from early use of the new melanoma medicines are another example. Therefore we are concerned that pressure to 'fast-track' medicines even more may lead to more morbidity issues such as these.

This may or may not be a deficiency of the Australian Regulators who evaluated the data they were given, but rather that there was pressure to follow the US and list medicines prior to the usual safety and efficacy data being mature. However it clearly demonstrates that, although the individuals on the Committees are trustworthy and hardworking, they can never be totally 'trusted' to make the right decisions[4]; this sometimes requires an external angle of examination. Nonetheless there are Regulators in other countries which are highly **respected,** including the FDA in the US, the EMA in Europe and the TGA.

Examples of TGA performance compared with other Regulators

The TGA, in common with all other Regulators, has made some better decisions than other respected Regulators.

E-cigarettes

Many tobacco companies are currently marketing nicotine containing cigarettes as a method for smoking cessation. In the US, UK and Europe they have been approved and are widely advertised; often shown on television in the context of young people at parties.

In fact, the data for their efficacy at smoking cessation are not strong and there is a major concern that young children will use e-cigarettes and progress to tobacco cigarettes. Further, there are increasing reports of hospital presentations for nicotine toxicity in children exposed to E-cigarettes in the home in these countries.

To date the **TGA has not approved e-cigarettes.**

A Fact sheet on the TGA website, updated on Oct 28th 2014, clearly states that they have not been approved by the TGA due to limited data on quality, safety and performance. It also warns that importing them via the internet is a punishable crime.

Australia has an excellent record for reducing smoking and this is a strong and appropriate position that has not been taken by the FDA or EMA

Dabigatran

The dangers of using dabigatran (and probably similar anticoagulants) without monitoring plasma concentrations were revealed in the recent BMJ article[5]. These were known to the Manufacturer but not given to "Trusted" Regulators which is very disturbing.

The TGA was not provided this information but, unlike the FDA and EMA which approved doses of 110 mg and 150 mg, the TGA also approved a 75 mg dose for high risk patients (the elderly and those with renal insufficiency) because the FDA knew that higher plasma concentrations and risk of bleeding and death were common in these patient groups. Further, it was anticipated that in Australia these medicines would be used predominantly by the elderly in whom clinical trial data was not available (i.e. for people in their 80s and 90s).

If the TGA had simply relied on decisions made by another Registry, the option to use a lower dosage form to minimise the risk of bleeding and death in higher risk patients would not have happened.

Metformin

Metformin is a medicine with a long and rollercoaster history. It is now the first choice of medicines for Type 2 diabetes mellitus and more than 100 million prescriptions each year are written worldwide. Lack of understanding by the FDA that metformin's pharmacokinetics and pharmacogenetics were very different to those of phenformin, which led the FDA to take metformin off their Register in 1977. It was only reinstated in 1995 following the results of new clinical research data although it remained widely used in Scotland and France.[4] Australians were able to be prescribed metformin throughout the period of time that it was not registered by the FDA.

Chapter 4 Regulation of Prescription Medicines

Issue 1 how may a trusted overseas regulator be defined?

As above – they cannot be defined as always 'trusted', but Australian regulators are made up of pharmacologists and clinicians expert in the Australian setting. The Australian research pharmacologists and pharmacists understand that a medicine that may be stable on the shelf in New York is not going to be in Cape York, for example

Point 3 If the TGA receives an application for registration of an NCE in Australia and the NCE has been approved by one trusted oversea regulator but rejected by another should the submission be assessed by the TGA?

2. Absolutely **YES**. As indicated above it would be essential to check the submissions to both countries and the reasons for their decisions. This is necessary to clarify if the decisions were based on the same data, different rationale or other local factors that may or may not apply to the Australian context. This is important because the populations are different (there are different markers on the immune cells which cause some adverse drug reactions and the genes that control clearance of the medicine out of the body are different), the age groups are different, the place of therapy is different and the co-ingested medicines are different, leading to different risks of side effects. Would a medicine that works in a group of Han Chinese be effective in European Australians? What about indigenous Australians – local pharmacologists have the best knowledge to predict the likely outcome in these groups not studied in the clinical trials.

Point 5. If a trusted overseas regulator rejects an application for marketing of a medicine for the same indications for which that medicine has been registered in Australia, should this spark a review by the TGA?

3. Absolutely **YES.** We would be surprised to learn that this isn't already the case (refer to the discussion above)

Page 4 Issue 2

Is there a good reason for Australia to impose additional requirements?

YES in various situations as illustrated by e-cigarettes and dabigatran above. Additional requirements should be imposed if there are population differences, if the therapy is to be used differently, where a better therapy is already available and using the new one would lead to worse clinical outcomes. These are decisions best made by practitioners and regulators at a local level.

- ***In summary to Section 4 we consider ALL NCEs should be fully submitted to the TGA to ensure safety, quality and efficacy in Australian conditions.***

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THEME 2: LACK OF FLEXIBILITY REQUIRED TO FACILITATE EARLY ACCESS TO INNOVATIVE PRODUCTS

This is a very complex and contentious issue. Early access to innovative products could benefit targeted patients, e.g. with cancer, but a rapid introduction might equally have harmful actions on patients. There has not been any published data showing the early access to medicines have improved patient outcomes. As pharmacologists sitting on hospital- and state-based adverse drug reaction

committees we see many poor outcomes for patients with these medicines who die of side effects in a hospital bed rather than having a reasonable quality of life at home. For the Pharma Industry to advocate for access to medicines prior to full investigations, and outside of a clinical trial, they need should present solid evidence to show real world data of where early access has helped outcomes. Our experience is that it worsens outcomes, and sometimes even because they are so sick, they are then ineligible for some types of palliative care (e.g. radiation for bone pain because they cannot tolerate the treatment).

IF the TGA were to fast-track approve a medicine on the basis of another Regulator it would need to have full access to their data and be funded to set up a Post marketing surveillance to provide invaluable information about both Efficacy and Safety in Australian patients.

However in this scenario the TGA would not be legally liable for any adverse situations that arose. The costs of this would also have to be contributed to by Pharma.

THEME 3: OVERLY BURDENSOME PROCESSES

We don't see that the current process is burdensome; if the Pharma is to make this statement it needs to be backed up with evidence. The process could possibly be streamlined but we have no data to suggest it is burdensome to patients, the main group of interest with this Review.

With regard to **generic** medicines we see no reason why a generic version manufactured overseas should not be rapidly introduced into Australia provide that:

1. It has demonstrated bioequivalence to the Australian product
2. The dosage forms are exactly the same.
3. It has been demonstrated **with a sample** that the comparator is ***identical*** to the Australian comparator
4. Any new issues discovered in the country of origin should be reported immediately to the TGA
5. Meets Good Manufacturing Practice (GMP) manufacturing standards (ie not contaminated by arsenic due to manufacture in a country where standards are less well regulated.)

With regard to Over-The-Counter (**OTC)** medicines we consider that the most important issues are:

1. Are they bioequivalent to each other
2. Are they clearly labelled in line with current Australian guidelines
3. Marketing and Advertising remains within Australian law.

In Summary

We Consider that:

The regulation of therapeutic goods should take a whole of lifecycle approach.

As a result, we agree with the Discussion Paper that the Regulatory System must:

- Have capacity to source and analyse data as it becomes available.
- Recognise and respond in a timely way to changes in the risk profile of products across their lifecycle.
- Provide for whole of life solutions, from product development to Withdrawal or Disinvestment.
- Be transparent and understood by all stakeholders, including Manufacturers and sponsors of therapeutic goods, Health Professionals, and Consumers.

We oppose the use of overseas Registries for NCEs.

This is because of:

- The high skills and performance of the TGA
- The need to be certain about Safety and Efficacy in the Australian population. The risk of Industry sending the results of approval from Regulator A when they know there is a hold up and potential rejection likely in Regulator B
- Finally history has taught us that early use of new medicines is as likely to cause harm as to produce the desired effect.

" Never be the first or the last to use a new drug" (Osler) [3]

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