Australian Government
Department of Health
Therapeutic Goods Administration

Reforms to the generic medicine market authorisation process

Consultation paper

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TGA Health Safety Regulation

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Introduction

Purpose

The Therapeutic Goods Administration (TGA) is seeking feedback on proposals to improve the generic medicine market authorisation process. Specifically, we are seeking feedback on possible reforms that would:

- reduce regulatory barriers for applicants seeking to register generic prescription medicines, while maintaining existing safety, quality and efficacy standards
- make the application process easier by making regulatory requirements clearer and more transparent
- support international work sharing opportunities
- provide incentives for specific generic prescription medicine applications, where these would support a more robust supply of medicines.

This consultation paper focuses on proposed reforms to market authorisation processes for generic medicines. Future opportunities may exist for similar changes to other prescription and non-prescription medicines processes, particularly those for biosimilar medicines.

Background

Role of generic medicines in Australia

A generic medicine is an additional brand of an existing prescription medicine. It contains the same active component as the existing medicine but may have differences in formulation. A generic medicine must also be 'bioequivalent' to the existing medicine. That is, the generic and existing medicine show no significant difference in the rate and extent of absorption of the active component after the same dose is administered. This means that it does not matter if you take the generic medicine or the existing medicine, you will experience the same therapeutic effect over the same amount of time when the same dose is taken.

Increasing access to generic medicines can provide Australian patients with greater choice and convenience and, in some cases, better value for money. Access to generic medicines is also important to ensure continuity of treatment, especially where a medicine shortage occurs.

The TGA's role in supporting generic medicine availability

The Department of Health aims to provide an affordable, accessible, efficient and high quality health system through regulations that protect the health and safety of the community while minimising unnecessary compliance burdens. We, the TGA, contribute to this aim through best practice regulation of therapeutic goods such as generic medicines.

Before any prescription medicine can be supplied in Australia, we evaluate the medicine with consideration of its safety, quality and efficacy. If approved, the medicine is entered on the Australian Register of Therapeutic Goods (ARTG). This process is known as 'market authorisation' or the prescription medicines registration process.

Not all approved medicines are available in Australia at any one time. It is up to the medicine sponsor to decide when supply of the medicine will start and cease. These decisions can be

based on cost, patent expiry timelines and other market considerations that are outside the TGA's influence or control.

Market authorisation for a medicine also does not mean that it will be listed for reimbursement on the Pharmaceutical Benefits Scheme (PBS). The decision to list medicines on the PBS is separate from the TGA market authorisation decision.

Changing landscape of generic medicines

There are many important medicines for which generic versions are difficult to develop. These include some types of formulations (e.g. liposomal injections), and medicines with certain routes of delivery (e.g. eye drugs); with active ingredients which cannot be easily characterised (e.g. polymers used to treat multiple sclerosis); which act locally (e.g. patches used on the skin); and those supplied with or in a delivery device (e.g. inhalation products). These have been called 'complex generics'.

Complex generics are more challenging to make, to test, and to establish bioequivalence to the existing medicine. The European Medicines Agency (EMA) and the United States Food and Drug Administration (US-FDA) have recently produced guidance material and conducted reviews as part of the development of appropriate regulatory systems for these medicines.

We are considering how the Australian regulatory framework should similarly evolve in response to such challenges.

This consultation paper explores opportunities to enhance the TGA's regulatory framework with the intention of better supporting the supply of generic medicines. These proposals outline possible improvements to the market authorisation process, as well as options to encourage applications for generic medicines of special interest. We are seeking your feedback on the proposals below.

Opportunities to improve the generic medicines market authorisation process

Reducing barriers through international alignment

The manufacture and supply of generic medicines is a global industry. Applicants who wish to register generic medicines on the ARTG must provide evidence to show that the goods meet Australian requirements for safety, quality and efficacy.

Many Australian standards are based on international standards, however further alignment with the processes of other regulatory agencies is possible. International alignment offers potential benefits through reduced regulatory burden, including by improving opportunities for work sharing with comparable overseas regulators. There are many potential benefits resulting from work sharing arrangements, assisting both the applicant and the regulatory agencies involved.

Changes to the Australian requirements for confirming bioequivalence is a possible area where greater international alignment in the regulation of generic medicines could be achieved.

Use of overseas reference product in bioequivalence studies

Demonstrating bioequivalence

A generic medicine must be bioequivalent to the existing medicine, also known as the reference product. The reference product is often the original innovator medicine.

Bioequivalence is demonstrated by conducting a 'bioavailability' study in which volunteers are given the reference product and, on a separate day, the generic medicine. The volunteers' blood is tested at different times, comparing how much of the active component in each medicine has been absorbed over time. To be bioequivalent, the absorption profiles must be the same.

Australia-specific requirements

Currently, the reference product used in the bioavailability study submitted to the TGA must be an existing medicine approved in Australia (the Australian reference product). This demonstrates that the generic medicine has the same safety and efficacy profile as the existing Australian medicine.

In some instances, an applicant has already performed a bioavailability study for market authorisation in a different country, and hasn't used the Australian reference product. A study using an overseas reference product may be acceptable to the TGA as long as the applicant provides evidence that the overseas reference product is identical to the Australian reference product.

To show that the overseas and Australian reference products are identical, applicants need to provide a range of information including:

- copies of labels and product information documents
- evidence that they have the same physical characteristics, such as tablet size, weight and colour
- evidence that they have exactly the same formulation
- if the medicine is a tablet or capsule, evidence that, they dissolve at the same rate.

Showing that the overseas and Australian reference products have exactly the same formulation can be challenging.

In some instances, 'identicality' to the overseas reference product cannot be established because samples of the Australian reference product cannot be obtained. This might be due to the medicine no longer being in supply or because it is made available only in limited supply.

When the Australian reference product can be obtained, not all medicine formulation details are publicly available. The specific ingredients are known, but the exact quantities of non-active ingredients are often confidential to the sponsor of that medicine. The company developing the new generic medicine will not have access to the information for either the overseas or Australian reference products. To show that the Australian and overseas reference products are the same, the generic company needs to reverse-engineer, or work backwards, to identify each ingredient in these products and their exact amounts. This can be difficult, and in some instances, not possible due to the complex nature of certain manufacturing processes and formulations.

Our requirements are largely consistent with comparable overseas regulatory agencies, such as those in Europe and Canada. However, some agencies such as those in Switzerland and Singapore, do not always rely on the same way of demonstrating 'identicality'. Under certain

conditions, there is less emphasis placed on confirming the exact quantities of the non-active ingredients. We are investigating whether similar approaches could also be applied in Australia.

Questions

Q1. Would changes to our requirements for demonstrating that Australian and overseas reference products are identical reduce barriers for applicants seeking to register new generic medicines?

Q2. Are there any potential unintended consequences of changing the data requirements when using an overseas reference product in a bioequivalence study submitted to the TGA?

Q3. Are there any other ways that we could reduce barriers through increased international alignment in the processes for obtaining market authorisation for generic medicines?

Increased clarity and transparency of regulatory requirements

Early advice on biowaiver justifications

Undertaking a bioequivalence study for a new generic medicine can be expensive and time consuming. Generally, all tablets and capsules need a bioequivalence study. However, there are some medicines and dosage forms that do not require this type of data.

There are also scenarios in which a justification for not submitting certain data may be sufficient. This is called a biowaiver, i.e. a waiver from performing a bioequivalence study where it would normally be needed. We may consider a biowaiver is appropriate for a particular medicine but the reasons for seeking it must be included in the dossier submitted to the TGA. Often the justification will include some scientific data.

For example, tablets containing an active component that is highly soluble and permeable (i.e. easily absorbed by the body) may be eligible for a biowaiver. When combined with the dissolution data for the tablet there may be little doubt that absorption occurs consistently. Scientific data demonstrating this may constitute an appropriate scientific justification for a biowaiver.

However, assessment of the scientific justification can be complex, and is considered case-by-case during the market authorisation process. If a justification for a biowaiver is not agreed during the evaluation, the only options are for the applicant to withdraw the submission or for the TGA to not approve the application.

There is currently no mechanism for applicants to seek formal advice on the appropriateness of a biowaiver justification prior to evaluation of the full dossier.

We are considering introducing means to allow applicants to seek formal scientific advice from the TGA on a proposed justification for a biowaiver. This optional step would happen prior to the applicant submitting a full market authorisation application and operate independently from the evaluation and registration processes. It would remove uncertainty about the acceptability of a proposed justification, before the full dossier is finalised and submitted. It may also reduce instances of unnecessary bioequivalence studies being performed.

Aspects to be confirmed include:

- what mechanism is available in the current regulatory framework for provision of formal scientific advice from the TGA
- what fees should be charged
- how to formalise the provision of advice.

It is important that the new process doesn't introduce any additional Australia-specific requirements and consequential regulatory burden.

Future consideration – advice on complex generic medicines

It is intended that in the first instance, advice is provided on a limited number of technical issues specific to biowaiver justifications for generic prescription medicines. In future, this list of topics could be extended to include issues particular to complex generics, and even more broadly in respect to other types of medicines or applications.

Questions

Q4. Would early advice from the TGA on biowaiver justifications be useful in compiling a dossier?

Q5. In what other ways can we increase transparency and clarity of regulatory requirements for generic medicine applications?

Supporting work sharing opportunities

Work sharing is a process where multiple regulators work simultaneously on different parts of a data package, when it has been submitted concurrently for evaluation in each country or jurisdiction. A joint evaluation report is then considered by each regulator to allow independent sovereign decision-making.

International work sharing provides us with an opportunity to avoid duplication of effort and leverage the work done by international counterparts. This can potentially enhance the decision-making process and reduce market authorisation timelines. Work sharing arrangements between regulators may also encourage global generic medicine sponsors to seek concurrent market approval in multiple countries or jurisdictions.

Participation in work sharing is a key objective in our international engagement strategy. We actively participate in international forums to progress work sharing and other global cooperation initiatives, including the Australia, Canada, Singapore, Switzerland (ACSS) Consortium and the International Pharmaceutical Regulators Programme (IPRP). The proposal below seeks to support these international engagement activities.

International templates

Using templates to submit information ensures consistency and helps make application requirements clearer. Templates can also serve as a checklist for applicants to ensure that a complete set of documentation is submitted.

Introducing internationally-used templates would support work sharing and reduce the regulatory burden on applicants by allowing them to submit the same information in the same format to multiple countries and jurisdictions. We have identified two international templates that may assist in achieving these goals.

- Bioequivalence trial information form:
  - A common template for bioequivalence study information has already been adopted by our ACSS partners Switzerland and Canada. This template allows applicants to consolidate key information about bioequivalence studies into one form.
- Biowaiver justification templates:
  - Many overseas regulatory agencies have country-specific requirements for biowaivers. A common template for biowaiver justifications may assist applicants in providing appropriate information in an internationally consistent way. This also increases the clarity and transparency of regulatory requirements. Biowaiver templates have already been developed by the International Pharmaceutical Regulators Programme (IPRP).

Questions

Q6. Will adopting these international templates improve opportunities for joint submissions to multiple agencies and hence work sharing?

Q7. Are there other ways of improving the generic medicines market authorisation process to support work sharing?

Generic medicines of special interest

In recent years the US-FDA has introduced a priority review process designed to prioritise submissions for generic medicines that would have a '*meaningful impact on generic drug access*'. US-FDA Guidance sets out eight public health priorities (or 'prioritisation factors') that may qualify a generic medicine for a prioritised review.

Some of these priorities are specific to the US context, for example '*submissions subject to special review programs such as the President's Emergency Plan for AIDs Relief*'; however, others may have relevance here. These include products in shortage, 'sole-source' drug products (i.e. in an Australian context, a drug product with a single sponsor and no blocking patents) and '*submissions containing certain patent certifications and exclusivity statements*' (in an Australian context amounting to a submission for a first generic with anticipated near-term patent expiries).

Critical differences in the public health systems in each country need to be acknowledged in any consideration of adoption of similar schemes in Australia. Therefore, we have conducted a preliminary investigation of two case studies below that may be applicable in our context.

Need for a robust supply of medicines in Australia

At times there may not be enough of a specific medicine in the Australian marketplace, leading to potential weaknesses in supply. These can be temporary medicine shortages or a long term reliance on only a small number of medicines to treat specific conditions. This can be a problem for the accessibility and affordability of medicines for patients and the Australian health system.

To achieve a more robust supply of medicines in Australia, we are considering possible incentives to encourage applications for new generic medicines of special interest. These medicines would be identified by their potential to address known weaknesses in supply.

It can be difficult to gauge the number of generic products available in the market place at any one time. Further, the number of goods registered on the ARTG is not indicative of the number of brands listed on the PBS.

Options for incentives

Aspects of the market authorisation processes can be tailored to encourage applications for generic medicines of special interest. These include:

- Time taken to evaluate, make a decision and register a medicine on the ARTG
- Fee structure for applications for registration of new generic medicines
- Data required to support an effective application
- Administrative requirements for submissions.

Our initial investigations have focused on the two case studies below, where a more robust supply of generic medicines may be beneficial to patients and the Australian health system.

Case study 1: Medicine shortages

Medicine shortages have become an increasing problem over recent years. The cause of medicine shortages is a complex and diverse interaction of many factors. These can include manufacturing problems, difficulties in procurement, global acquisition of sponsor companies, political instability and natural disasters.

Australia accounts for only 2% of the global pharmaceutical market and imports over 90% of medicines. This makes Australia particularly vulnerable to medicine shortages arising from factors outside our control.

Some medicines imported to Australia are only manufactured at one location, even if they are supplied by many companies. Other medicines may be manufactured in multiple locations but supplied by only one company. Both scenarios present a risk of medicine shortages in the event of, for example, natural disasters and global economic crises.

We recently introduced mandatory reporting of medicine shortages for all prescription medicines as well as other medicines which are vital for public health. This included the introduction of a Medicine Watch List of products which, if in shortage, are automatically considered to have a critical impact. Under the new law, medicine sponsors must also report shortages that will not have a severe impact on patients.

There are actions that we take in response to a medicine shortage, including arrangements for alternative sources of supply once it is recognised. A more proactive approach would be to diversify supply by encouraging more generic versions of these medicines to be registered on the ARTG, particularly those with only one supplier or manufacturer. This could reduce the likelihood of medicine shortages happening.

Case study 2: Medicine expenditure

The cost of medicines is a significant burden for the Australian health system. The pricing of medicines is complex. Typically, a medicine containing a new active component is launched under patent. It may have a certain price until the patent expires and competition or generic

products emerge. The price of a medicine following patent expiry usually decreases rapidly. In Australia, the listing of a 'first new brand' (i.e. a first generic medicine) on the PBS will result in an automatic 25% price reduction and ongoing Price Disclosure reductions.

The pharmaceutical patent landscape is complex and operates within an international environment. Some prescription medicines may be associated with patents covering the active component, modified forms of that active component, combinations of known active components, particular formulations (tablets, topical forms) and dosage regimens. These aspects can affect patent expiry times and create opportunities for patent extensions.

The key factors impacting supply appear to be the patent expiry date and the PBS submission deadline. Sponsors often apply for new generic medicines well in advance of patent expiry. We evaluate and can register the medicine on the ARTG; however, the medicine cannot be supplied until after that expiry date. In some instances, the gap between registration and supply can be months or years. There will also be a delay before the medicines can be listed on the PBS.

Increasingly, the 'first new brand' on the PBS is sponsored by the same company as the innovator brand, or by an affiliate. In these instances, patent considerations are not relevant.

We are considering implementing a priority system where applications could be either evaluated more quickly or go to the head of the evaluation queue. However, given the complexities outlined above, this may not result in a generic medicine being available more quickly on the PBS.

Questions

Q8. Is it appropriate to offer incentives to medicine sponsors to bring more generic medicines to Australia?

Q9. Should we offer incentives to medicine sponsors to address medicine shortages and medicine expenditure?

Q10. Are there any other examples where a more robust supply of generic medicines may be beneficial to patients and the Australian health system?

Q11. What incentives should we pursue in order to create a more robust supply of medicines?

Summary

We are investigating a range of options to improve the generic medicine registration process. We are now seeking feedback and suggestions on these options.

Questions

Q12. Are there any other options for improvements to generic medicines market authorisation processes that would:

- reduce regulatory barriers through greater international alignment with comparable overseas regulators
- increase clarity and transparency of regulatory requirements
- support international work sharing for generic medicines
- support a more robust supply of medicines?

Next steps

After the closure of this consultation period, we will consider feedback and initiate further consultation with interested parties on implementation of supported options. This would include seeking comment on more specific details for each proposed reform.

Implementation of many of these options will require updating business processes and administrative requirements, and potentially regulatory changes. Therefore, careful consideration of these options is needed.

Version history

Version	Description of change	Author	Effective date
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