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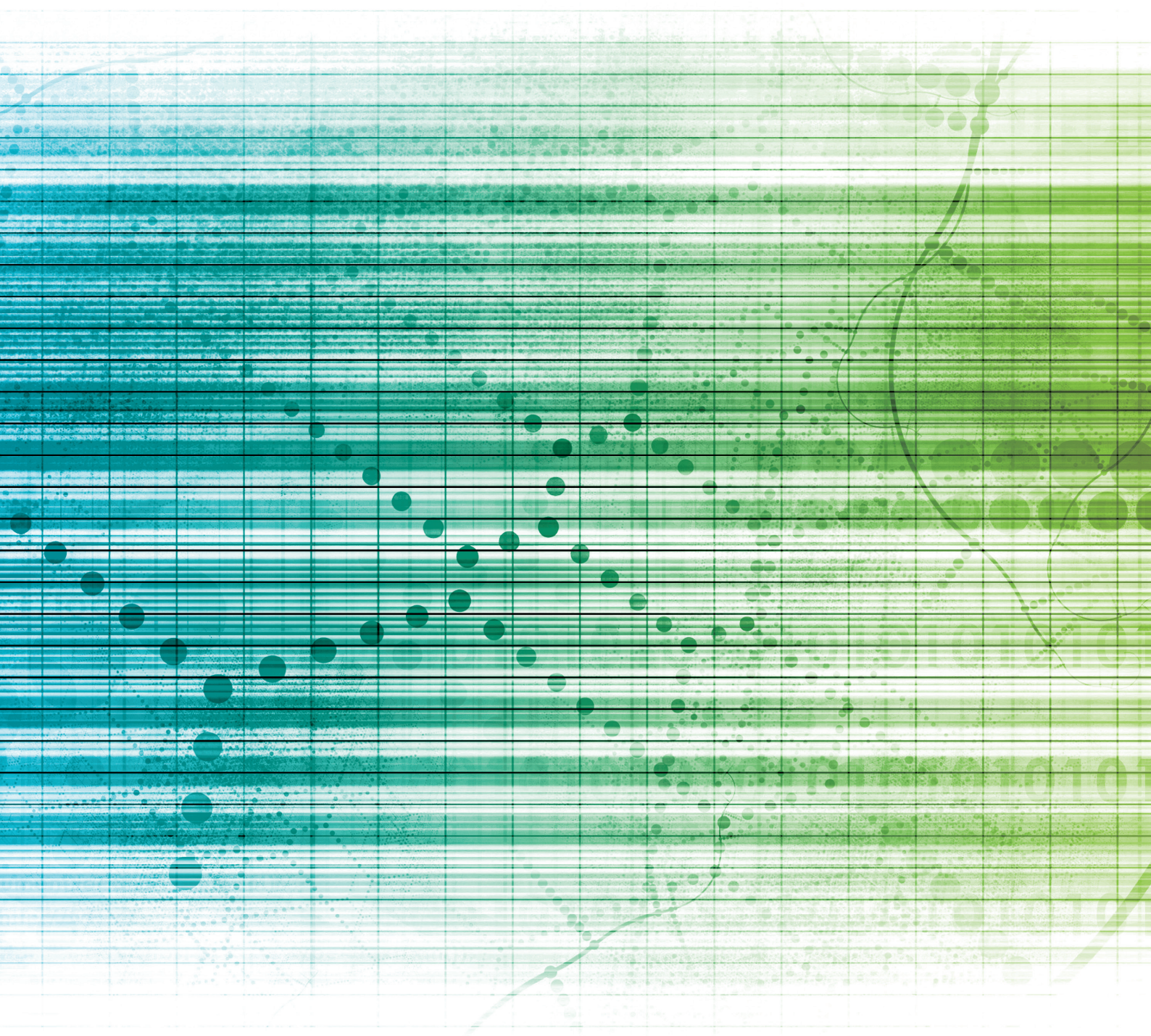


Guide to BIOSIMILARS

Introduction

The introduction of high quality generic medicines has made a significant impact in reducing healthcare expenditure in Australia. These lower cost alternatives to expensive, brand name medicines have helped contain expenditure through the Pharmaceutical Benefits Scheme (PBS) and have allowed better access to important medicines for a greater number of patients.

Biosimilars are now able to offer alternative treatment options to many expensive biological medicines, with the potential for considerable cost saving.

The substantial benefits associated with biosimilars could, however, only be achieved if mechanisms are available to support their entry into the market. Slower introduction of biosimilars into clinical practice will result in a failure to realise the expected savings to healthcare and may increasingly restrict access to medicines.

Biological Medicines

Biological medicines are an important and relatively new category of medicines that are derived from living organisms using biotechnology and can be used in the treatment, prevention or diagnosis of diseases and medical conditions. Unlike most traditional, small-molecule prescription medicines that are made through chemical processes, biological medicines are generally made from living materials. Biological medicines are usually larger and have a more complex structure than most small-molecule prescription medicines.

Biological medicines are the fastest-growing segment of the PBS, accounting for $1.3billion (15%) of PBS expenditure in 2013. The importance of biological medicines to healthcare budgets, as well as to the pharmaceutical industry and its revenues, cannot be overstated. Worldwide, there are more than 200 biological medicines on the market today, with around 300 more being investigated in clinical trials.

For more than 20 years Australian patients have benefited from the availability of biological medicines. These medicines have revolutionised the management of some of the most difficult to treat diseases and have helped to prolong and improve the lives of many patients. Some examples are:

- Hormone products, e.g. growth hormone for growth **hormone disorders**, erythropoietin (EPO) for **anaemia** and other diseases, and insulin for **diabetes**
- Immunomodulators such as beta interferon for **multiple sclerosis**
- Monoclonal antibodies (mAbs), an important class of medicines used to treat and many conditions including **cancer** and **rheumatoid arthritis**, **multiple sclerosis** and other **autoimmune** diseases
- Blood coagulation factors, e.g. factor VIII and IX for blood disorders such as **haemophilia**
- Enzymes for the treatment of a variety of conditions, including metabolic disorders such as **Gaucher's disease**
- Vaccines for the prevention of many diseases, such as those caused by **human papillomavirus** infections

However, these biological medicines are very costly to the PBS, which may limit their availability to some patients.

What are Biosimilars?

When relevant patents have expired, biological medicines can also be marketed by companies other than the company that originally marketed the product. This novel subclass of biological medicines is most commonly known as 'biosimilars', which is the term used throughout this booklet. In other texts they may be named 'similar biological medicinal products', 'biosimilar medicines', 'follow-on biologics' or 'similar biotherapeutic products'.

Biosimilars are a subclass of biological medicines, with comparable quality, safety and efficacy to that of originator reference biological medicines.

Biological Medicines

Medical products made from a variety of natural sources (human, animal or microorganisms) that can be used in the treatment, prevention or diagnosis of diseases and medical conditions

Originator Biological Medicines

Used as reference biological medicines for the development of biosimilars

Biosimilars

Biological medicines that can be marketed once the relevant patents of the originator biological medicines have expired

BIOSIMILARS ARE IMPORTANT

Some manufacturers of medicines have the scientific capability to produce similar versions of biological medicines – biosimilars. Once the relevant patents have expired, biosimilar manufacturers are able to bring these more affordable versions of biological medicines to Australian patients. Through a rigorous process of development and regulatory evaluation, biosimilars are now being approved by the Therapeutic Goods Administration (TGA) as being comparable in quality, efficacy, and safety to the original biological medicine.

Biosimilars are Important for Patients

Patients in Australia deserve access to effective and affordable biological medicines as they fight disabling and life-threatening diseases. Biosimilars can help to improve patient access to these biological medicines. The potential savings that can be expected by the introduction and uptake of biosimilars in Australia are likely to result in more patients having access to the medicines they require. Furthermore, patients can be confident that these products are assessed and approved for use in Australia by the TGA the same scientific authority that approved the original biological medicine and, in fact, approves all medicines marketed in Australia.

Biosimilars are Important for Clinicians

Biosimilars offer clinicians an affordable and therapeutically equivalent alternative to essential but expensive biological medicines.

The scientific principle of the development of a biosimilar is a thorough comparability assessment of quality, safety and efficacy, which aims to demonstrate the similarity of the biosimilar with the originator biological medicine, known as the reference product. Once successful and complete comparability has been demonstrated for a particular biosimilar, then, as a result, the quality, safety and efficacy profile established for the relevant reference product is also applicable for the biosimilar.

The TGA grants successful product applications a marketing authorisation for Australia. This approval allows a medicine to be sold in Australia and is based on the TGA's positive scientific opinion following assessment of the data package. Therefore, all biosimilars are approved only after extensive and rigorous regulatory evaluation of their registration data, which will always include a full comparability assessment.

Biosimilars provide physicians with the opportunity to prescribe high-quality and cost-effective medicines for the benefit of their patients.

Biosimilars are Important for Pharmacists

Pharmacists have a leading role in ensuring that the most appropriate medicines are made available to the right patients at the right time. In doing so, pharmacists are acutely aware of the burgeoning cost of biological medicines and are often tasked with helping to manage healthcare budgets as effectively as possible.

Biosimilars offer an affordable alternative to more expensive biological medicines and can help pharmacists to improve patient access to these important medicines while helping then to manage their community or hospital pharmacy budgets.

Pharmacists have a major role to play in critically appraising biosimilars and making recommendations for their use in clinical practice. Pharmacists should be assured by the robust regulatory systems and pharmacovigilance requirements that are in place in Australia to ensure that all medicinal products meet the required standards for quality, safety and efficacy.

Biosimilars are Important for the Pharmaceutical Benefits Scheme (PBS)

Biosimilars offer therapeutically equivalent and more cost-effective alternatives to existing, high-cost biological medicines. This means that more patients can be treated within the same budget, or that savings can be made in order to fund other treatments.

Biosimilars provide a unique opportunity to help manage the growing costs of biological medicines on the PBS. In the same way that generic versions of conventional chemical medicines are now very widely used in Australia at levels far greater than during their original introduction in the 1980s, we can anticipate similar uptake in time with biosimilar versions of biological medicines.

Biosimilars are Important for Politicians and Policy Makers

Biosimilars bring additional competition to the Australian pharmaceutical industry, in the same way generic pharmaceuticals bring competition to the non-biologic product landscape. Through this competition, the cost of healthcare can be reduced and more patients can gain access to essential biological medicines. Competition stimulates further innovation in the Australian pharmaceutical industry. These benefits should encourage politicians, advisers and policy makers to continue their current support for the appropriate regulation and rapid introduction of biosimilars into the Australian healthcare market.

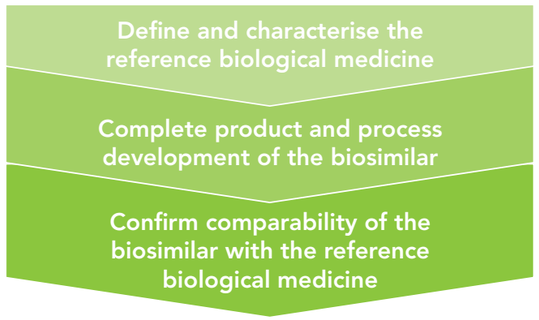
Although the TGA is the regulatory body that conducts the scientific assessment process and grants successful product applications a marketing authorisation, it is the role of the Pharmaceutical Benefits Advisory Committee to recommend listing of a product on the PBS. It is therefore vital that a predictable market entry pathway for biosimilars is created with consistent regulatory and reimbursement requirements to encourage biosimilar market entry.

Biosimilar Development and Manufacturing

Biosimilar medicines are developed to match their reference product in terms of quality, safety and efficacy.

Development of a biosimilar can cost $20 million to $200 million and take up to 10 years[1], which is approximately 15 – 200 times the cost of development of small molecule generic medicines.

The basic principle underlying the development of a biosimilar is comparability with the reference product. This is not a new scientific concept that applies only to biosimilars. Comparability, as assessed through a process known as a 'comparability exercise', is a critical concept that has been evolved in order to perform comparisons between different versions of any new biological products in development. Data provided by such comparisons are needed to show that there are no significant differences in quality, safety and efficacy between the different versions of the product under development.



Because they are produced from living organisms, biological medicines generally have more variability than traditional chemical drugs. In fact, biological medicines of all kinds have some variability between batches, even when manufactured by a single company. Therefore, the goal in creating a biosimilar is to make a safe therapy that treats a disease the same way as the original biological medicine.

After any product has been approved by the TGA, it is not unusual for further changes to be made in the manufacturing process. When changes are made, the manufacturers of the product are required to demonstrate that the safety and efficacy of the products remains comparable to those of the product prior to the implementation of the manufacturing change.

Biosimilar development involves testing techniques that are often more sophisticated than those used for the reference products which likely would have received approval 10 to 20 years earlier.

Biosimilar medicines are manufactured according to the latest state-of-the-art technology, ensuring the highest quality standards available.

Biosimilar Regulation

Biosimilars, as with all biological medicines in Australia, undergo rigorous regulatory and scientific assessment by the same scientific expert committees of the TGA.

The application for a marketing authorisation for any biotechnology-derived product must be submitted to the TGA and be assessed according to Australian guidelines and other relevant international guidelines adopted by the TGA.3 To encourage biosimilar market entry, it is vital that the TGA process is predictable and in line with the regulatory requirements of international regulators, particularly the European Medicines Agency (EMA). To date the EMA has had the greatest experience among the highly regulated regions in bringing biosimilars to market.

All pharmaceutical companies are legally required to continuously monitor the use and effects of all their medicines. They must have systems in place to collect, detect, assess, understand and communicate any adverse reactions or any other medicine-related problem. The science and activities of these processes are known as 'pharmacovigilance'.

The sponsor of a biosimilar must conduct laboratory and clinical studies to show that the biosimilar is sufficiently similar to the original biological medicine and meets appropriate quality standards of production. The information from these studies is submitted for the TGA's review to ensure that, as far as possible, the biosimilar medicine and the original biological medicine are sufficiently alike, so that in terms of benefits (and risks) similar outcomes may be expected from the biosimilar.

All biological medicines, including biosimilars follow the same pharmacovigilance rules.

Once medicines are marketed, the company must prepare and submit to the TGA, regular reports providing detailed information on available safety data. These are known as Periodic Safety Update Reports (PSUR). The purpose of these reports is to detect any change in the risk-benefit balance of a medicine.

International Experience with Biosimilars

Patients and governments around the world are benefiting from the use of biosimilars.

In Europe there are now 21 approved biosimilars on the market that have delivered price reductions of 15 to 30%[4]. However, biosimilars have not experienced rapid market share acquisition. Australia should therefore expect slower price reduction and fewer savings to be delivered from the market entry of biosimilars, in the absence of market uptake drivers, compared to those realised when generic medicines enter small molecule markets.

In order for Australia to realise all the benefits of biosimilars it is important that market uptake drivers are implemented to encourage the use of biosimilars.

Extrapolation of Indications

Biological medicines are often used in more than one indication. For example, a monoclonal antibody might be indicated (that is, approved for use) for rheumatoid arthritis and multiple sclerosis. The mechanism of action for these various indications is very often the same. Therefore, it may be possible that the demonstration of clinical similarity proven by a biosimilar for one indication can be 'extrapolated' to other indications.

This fact has been acknowledged by the European regulators and therefore they have included a provision for this in the European regulatory framework for biosimilar medicines, which states that "in certain cases it may be possible to extrapolate the therapeutic similarity shown in one indication to other indications of the reference medicinal product"[5].

The scientific basis to this extrapolation of indications is the proven, in-depth comparability between the biosimilar and the reference product at quality level. This quality comparability is established with regard to functionality and must be demonstrated with comprehensive analytical characterisation, relevant receptor binding studies, bioassays and appropriate animal studies, all to be performed with the biosimilar and the reference product in a rigorous comparative manner.

Extrapolation of indications reduces the development costs of biosimilars and those savings are passed on to governments, pharmacists and patients.

Interchangeability

Interchangeability refers to the medical practice of changing one medicine for another that is equivalent, in a given clinical setting on the initiative or with the agreement of the prescriber.

A medicine is considered to be interchangeable if it can be administered or dispensed instead of another clinically equivalent product. The regulatory scientific data, published via the AusPAR (Australian Public Assessment Report), should guide prescribers' decisions on interchangeability.

In the context of interchangeability it should be noted that if an originator company changes the manufacturing process of an existing product, interchangeability between the pre- and post-change products is accepted as long as the change is supported by a package of comparability data that reviews the pre- and post-change product. The same approach needs to be taken for biosimilars, based on the comparability data with a reference product.

The extensive comparability data, and also post-marketing data, will therefore demonstrate that it is safe and efficacious to switch dose for dose from the reference product to the biosimilar.

Substitution

Substitution refers to the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without requiring consultation with the prescriber.

Substitution of small molecule originator brands with affordable generic medicines in Australia at the point of dispensing has resulted in major savings in PBS expenditure for the government. However at this point in time, a clear process has yet to be developed to establish a suitable pathway for substitution of biosimilars.

The TGA's current policy is that substitution of a biological reference product with its biosimilar is inappropriate without a physician's prescribing decision. "Because all biotechnology-derived products are inherently variable, the established safety record of the reference product does not necessarily apply to the biosimilar."[5]

The Australian policy regarding substitution of brands needs urgent review given the inherent batch-to-batch variability of biological reference products and the in-patient biosimilar data that are now available following years of international physician experience and real world evidence.

It is important to note that a change between a reference product and its biosimilar does not change quality of patient care or clinical management. Even switching between different originator products is common in clinical practice without raising concerns, despite lack of data related to these changes[6].

References: 1. Federal Trade Commission Report, June 2009. **2.** European Commission, What do you need to know about Biosimilar Medicinal Products, p.8, April 2013 http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf. **3.** TGA - http://www.tga.gov.au/industry/pm-argpm-biosimilars-01.htm. **4.** Saving money in the European healthcare systems with biosimilars. Haustein et al. Generics and Biosimilars Initiative Journal (GaBI Journal). 2012;1(3-4).120-6. **5.** TGA - http://www.tga.gov.au/industry/pm-argpm-biosimilars-09.htm. **6.** Ebbers et al. Expert Opin Biol Ther 2012.

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