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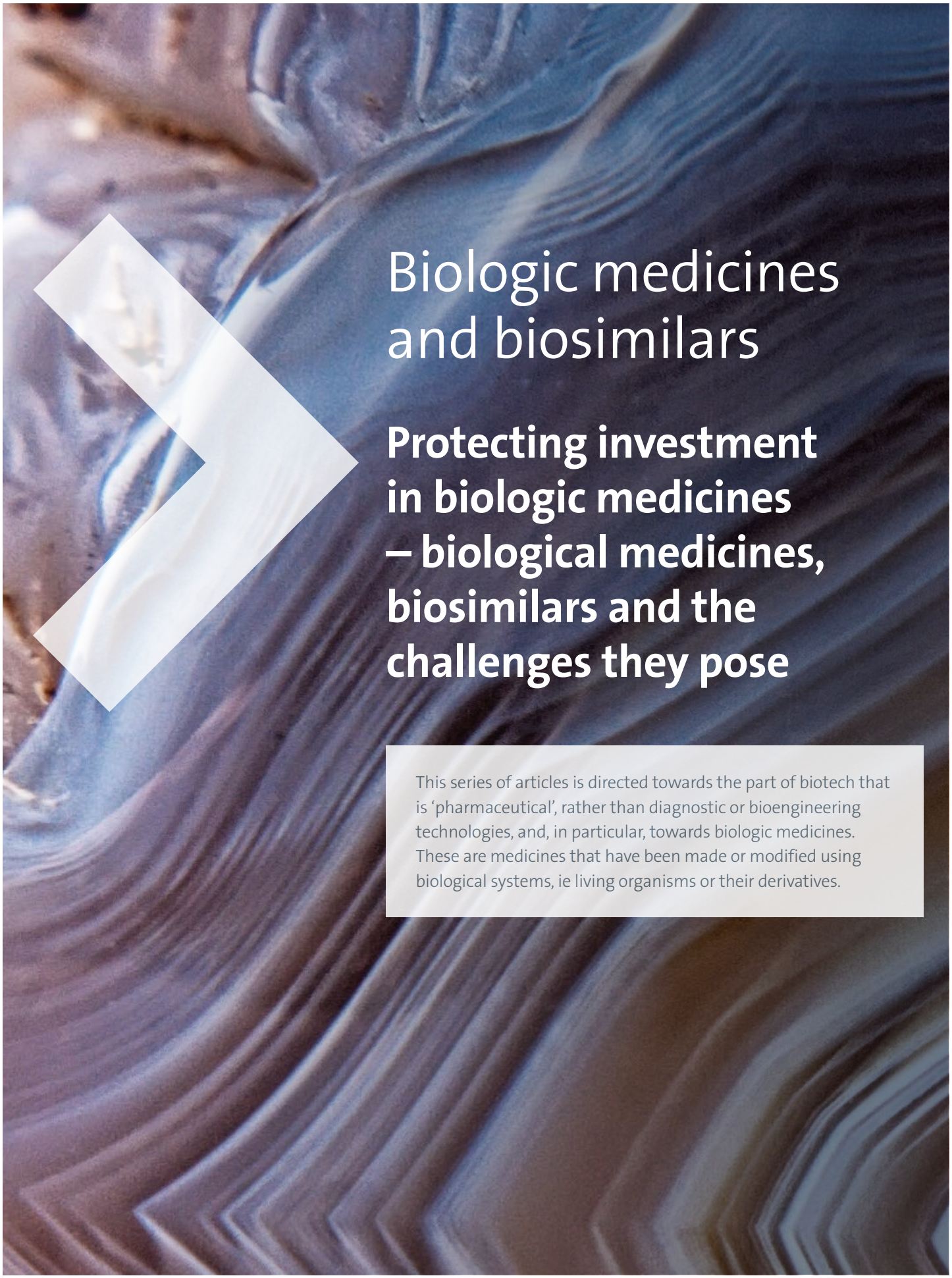

Biologic medicines and biosimilars

Protecting investment in biologic medicines – biological medicines, biosimilars and the challenges they pose

This series of articles is directed towards the part of biotech that is 'pharmaceutical', rather than diagnostic or bioengineering technologies, and, in particular, towards biologic medicines. These are medicines that have been made or modified using biological systems, ie living organisms or their derivatives.

In the context of pharmaceutical development, biologic medicines have been around for a long time – long enough for there to be at least nine blockbuster biologic medicines that have lost, or will lose, patent protection in the period 2014 to 2019.

TABLE 1 – Examples of well-known biologics

Product	Biological class	Therapeutic use
Humira®	Monoclonal antibody	Crohn's disease
Enbrel®	Monoclonal antibody	rheumatoid arthritis
Avastin®	Monoclonal antibody	metastatic cancers
Remicade®	Monoclonal antibody	autoimmune diseases
Herceptin®	Monoclonal antibody	metastatic breast cancer
Rituxan®	Monoclonal antibody	non-Hodgkin's lymphoma
Lantus®	Longacting insulin	diabetes
Neulasta®	Granulocyte-colony stimulating factor (G-CSF)	white blood cell growth
Epogen®	Erythropoietin	anaemia
Genotropin®	Human growth factor	growth failure in children
Gardasil®	Protein sub-unit vaccine	human papilloma virus
Glybera®	Hybrid virus vector	lipoprotein lipase deficiency

The maturity of the sector, including the end of monopoly protection provided by patents and data exclusivity, means that 'copies' of biologic medicines are presenting an ever-increasing challenge in the regulatory space. Due to the involvement of biological systems in the manufacturing processes, these 'copies' are similar but not identical. When they deliver clinical, safety and efficacy results comparable to the original biologic medicine 'reference' product, they are said to be 'biosimilar'.

Recent developments have focused the attention of policy makers, legislators, industry players and health care consumers on this area:

- new marketing authorisations (Therapeutic Goods Administration (***TGA***) registration) of biosimilars. Examples including (through its acquisition of Hospira) Pfizer's biosimilar infliximab (Inflectra) – the first monoclonal antibody biosimilar therapy to be registered in Australia – and Eli Lilly's biosimilar insulin glargine (Basaglar);
- conflicting decisions between Australia's medicines regulators about the reimbursement approval processes for biosimilars and, in particular, what is required for interchangeability;
- the treatment of intellectual property protection schemes for biologic medicines under the Trans Pacific Partnership Agreement; and
- the Australian High Court's decision in *D'Arcy v Myriad Genetics Inc*[1], relating to gene technologies, limiting the scope of what may be patented in the biotech space.

1 ***D'Arcy v Myriad Genetics Inc*** [2015] HCA 35.

This interest is unsurprising. In data released on 1 August 2016, biologic medicines currently comprise six of the top 10 medicines (by cost between July 2014 and June 2015) subsidised by Australia's reimbursement scheme, the Pharmaceutical Benefits Scheme (***PBS***), treating a range of conditions spanning arthritis, cancer and diabetes. They currently cost the Federal Government approximately $2.3 billion per year, with $1.1 billion associated with the six referred to above. Biosimilars are seen as an important part of reducing the cost impact of biologic medicines. They are generally assumed to introduce competitive products that can challenge the pricing points set by the original supplier of the biologic medicine, leading to improved access to medicines and significant cost savings to the PBS scheme.

How are biologic medicines different and what are the implications of this?

The effect of most medicines is by the action of a small molecule – the active pharmaceutical ingredient. Small molecules are inherently well-defined chemical entities and can be copied with great precision – a 'generic' version.

Worldwide, generics have driven a huge reduction in the cost of medicines, enabled significant businesses to thrive on the back of the provision of generic pharmaceuticals and threatened the business models of established pharmaceutical companies. This is possible because they are almost always interchangeable – it makes no difference to the patient which product is taken – and hence the generics can be true competitors with the original products.

For follow-on biologic medicines to have the same impact and provide the economic benefits associated with the end-of-monopoly protections, they, like generic medicines, will need to compete across the range of uses and be interchangeable with their reference products.

However, for biologic medicines, the concept of a copy is not really apt. Biosimilars are produced using different biological sources, different biological processes or different conditions from those used to prepare the original reference biologic. These differences can produce different products.

Many biologic medicines act by mediating the immune system. Even small differences can present safety and efficacy risks. Further, additional risks can arise from switching between biosimilar products. This is particularly the case for biologic medicines where the mode of action is not well understood or when the role of the differences in structure, or the lack of detailed structure, means the potential for different immunological responses cannot be readily assessed.

Consequently, it is better to understand the development of these 'copies' under the broad umbrella of ***'follow-on biologics'***. This allows for those copies that offer clinical improvements – or, as they are sometimes termed, ***biobetters*** – to be distinguished from ***biosimilars***, which are intended to deliver clinical, safety and efficacy results comparable to the original biologic 'reference' product. Also distinguishable are those biosimilars that can be considered safely ***interchangeable*** (in the same way that generic medicines are generally considered to be) for patients.

The consequence of this lack of 'identicalness' of followon biologics is broad reaching. It has the potential to impact on whether they will deliver the same cost benefits and business impact that generic pharmaceutical businesses have. These factors appear to have the effect of reducing the market penetration of followon biologics. Three aspects are worth exploring.

Protection for biologic medicines

The developing, and globally diverging, patent protection position for biological innovation may result in the more limited patent rights that biologics can obtain being more difficult to enforce in meaningful ways. For example, where the underlying therapeutic innovation is not patentable due to an exclusion that exists in a particular jurisdiction, the lack of 'identicalness' to the patentable product may enable the follow-on product to avoid infringement and enter the market earlier than would be expected. This in turn has the potential to impact on investment in innovative biologic medicines by undermining the economic benefits provided by a patent-based monopoly. In some jurisdictions, this has resulted in the development of separate mechanisms, such as the US data exclusivity/market exclusivity arrangements for biologic medicines, which provide 12 years' protection independent of patent rights.

Assessment of biosimilars

Regulators involved in providing marketing authorisation typically take a cautious approach to follow-on biologics, and impose different and additional requirements than those for approving generic versions of small molecule medicines. However, the extent and nature of the differences are not consistent from one regulator to another, or, indeed, with the same regulator for different products. The uncertainty as to what is required to obtain biosimilar registration extends to the indications for which the follow-on products will receive marketing authorisation – this will not always be the same as for the reference biologic – and the use of naming identifiers for each biosimilar product.

Improving access and affordability

If the path to the commercial success of follow-on biologic medicines is to work in the same way as for generic drugs – delivering true competition and providing real pricing impact for reimbursement funding – the follow-on product needs to be not only biosimilar but also interchangeable with the original biologic medicine. The lack of 'identicalness' means that interchangeability is a fiercely contested matter.

These issues, explored in more detail below, render the timing of entry of followon biologics uncertain, and present very different risk/reward calculations for those bringing them to market. In turn, this means business models very different from those promoting generics are required.

This is difficult enough in jurisdictions where clear statutory pathways to registration exist and the monopoly protection provided by the combination of patents and exclusivity is certain. In Australia, recent changes to obtaining marketing authorisation and reimbursement approval schemes have resulted in approaches that are not only less clear but also out of step with other major economies. Arguably, as a result of the *Myriad* decision, Australia's patent protection is similarly uncertain and out of step. When coupled with the already low level of certainty in the sector, there is a risk that Australia will not benefit from access to biosimilars to the extent it otherwise might.

Protecting investment in medicines

The last several years have seen a number of legal challenges, particularly in the US and Australia, to the validity of patents covering biologic products and their uses. As a result, there has been pressure to provide alternative protection, usually in the form of extended data exclusivity or market exclusivity as a way of ensuring a return on investment in new biologics. Patents provide that economic benefit by providing a monopoly right to exploit the patented product or process. Data exclusivity prevents others from relying on the clinical trial, and other data provided in support of the original biologic medicine, to obtain marketing authorisation for a specified period of time. Market exclusivity prevents others from obtaining marketing authorisation of a follow-on biologic for a specified period of time, regardless of whether it is necessary to rely on data provided in support of the original biologic medicine to obtain marketing authorisation.

What protection is normally relied on in the medicines space?

To understand the particular challenges for originators posed by biologics, it is useful to understand what is considered 'normal' when it comes to encouraging investment in medicines and what is different for biologic medicines.

There are three key legal or regulatory barriers to entry in the medicines space. These are ***patents,*** requirements for both ***marketing authorisation*** – addressing safety and efficacy issues – and ***reimbursement approval*** – primarily a matter of cost but with particular jurisdiction-based schemes providing a range of incentives and disincentives to market entry.

Patents

In the case of small molecule medicines, patent protection is generally sought for each of:

- the active ingredient or classes of active ingredients – the chemical entity (or class of chemical entities) that have the pharmaceutical effect;
- formulated products – the particular dose (or dose range) together with particular formulation details, including the non-active excipients or absorption-modifying excipients that assist with ensuring that the pharmaceutical effect is optimised, such as modified release profiles;
- methods of treatment, being dose and frequency of administration details for the treatment of particular diseases or medical conditions, sometimes together with details of physiological parameters that can be used to modify and optimise treatment; and

- processes for making or isolating the active ingredient or the formulated products actually sold.

As long as a patent remains in force, only the patent owner and those it authorises may produce or market products covered by the claims of the patent.

Marketing authorisation barriers

In all major economies, the marketing of medicines (and other therapeutic goods) is subject to strict regulation. This generally requires satisfying the relevant National Registration Authority (***NRA***) that the product is safe and efficacious and manufactured to a sufficient quality, thereby qualifying for 'marketing authorisation'. In the US, this is the Food and Drug Administration (***FDA***). In Europe, it is the European Medicines Agency (***EMA***). In Australia, this is the role of the TGA. In Australia, the specific requirement for pharmaceuticals is that the product is 'registered' on the Australian Register of Therapeutic Goods.

In order to satisfy the relevant NRA, detailed clinical trial data, together with a range of non-clinical studies, must be provided by the sponsor of the medicine. The studies required and the preparation of the applications for approval are expensive and time consuming. Much of this information is not in the public domain and is provided to the relevant NRA on a confidential basis. The need to provide extensive supporting data provides a barrier to entry for those wanting to market a competing version of the medicine.

Due to the cost and the ethical issues associated with repeating clinical studies, it is generally accepted that those wanting to market competitor versions ought to be able to rely, at least to some extent, on the data provided by the original sponsor. As a result, the requirements can be simplified to proving that the product is relevantly the same (thus, safe and efficacious) and manufactured to an acceptable quality.

The balance between the competing interests of the original sponsor and those wishing to compete is usually provided by imposing restrictions on how the NRA can use the confidential information – data exclusivity – and in some jurisdictions by providing periods of market exclusivity, sometimes as a reward for meeting particular market needs, including bringing drugs for limited purposes (orphan drugs) or populations (eg paediatric use).

In addition to these specific barriers and restrictions, the very process of obtaining marketing authorisation is time consuming and, in some jurisdictions, uncertain, providing a further barrier to entry. In some jurisdictions, there are clear statutory pathways that govern the process of obtaining marketing authorisation, which set out different pathways for different types of applications. In such schemes, the pathway for the original product can be very different for the competing, or generic, product.

In Australia, there are no separate statutory pathways for new and generic products or, indeed, any detailed statutory pathways for registration. The only strict requirement is that the decision maker be satisfied that the product is safe and efficacious and of an acceptable quality. The details of the specific requirements are provided by way of TGA guidance. Notably, this adopts much of the EMA's requirements, but modified for Australian conditions. This means that the Australian process has different, and often additional, requirements to the overseas requirements, and applicants have less certainty about the approval process. However, most medicines are brought to market globally, and these differences can cause issues, especially as Australia is a relatively small market.

Reimbursement approval and interchangeability

Once a product achieves marketing authorisation, sales depend on someone being prepared to pay for it. However, many medicines would be unaffordable for those who need them.

Various schemes around the world subsidise the use of medicines – collectively termed 'reimbursement approval'. However, there are almost as many different schemes as there are jurisdictions. These range from insurance-based schemes, where the sponsor for a product needs to convince health insurance providers to include its product in the insurer's scheme, to government-supported schemes such as Australia's PBS, where a medicine is subjected to cost-benefit analysis by a statutory committee, the Pharmaceutical Benefits Advisory Committee (***PBAC***), before the government decision maker can decide to subsidise (or 'list') the medicine on the PBS.

Obtaining reimbursement approval is usually critical for the success of a product. Those seeking to provide competing products need to ensure that their products can be reimbursed in the same way as the original product. This generally requires the product to be interchangeable with the original product, thereby allowing the products to be swapped for each other without any input from health care professionals. The processes for obtaining the coveted interchangeable status are, like reimbursement approval, diverse. Despite the diversity, for small molecule medicines, it is generally accepted that proof of bioequivalence is sufficient to permit interchangeability.

In Australia, decisions regarding interchangeability are connected to the reimbursement process by which interchangeable medicines are 'a-flagged' on the PBS, indicating that they can be substituted by the dispensing pharmacist without reference to the prescribing healthcare professional. Until recently, it was considered that this would only occur where the products were considered by the TGA to be bioequivalent.

What protections are available for biologics?

Patents

Generally, patent laws are harmonised in the form of the TRIPS Agreement (Agreement on Trade-Related Aspects of Intellectual Property Rights), which provides that patent laws should largely be technology neutral. In summary, patent laws generally do not explicitly exclude biologic medicines from patent protection. However, with the individual, the development of laws in different jurisdictions means that certain types of claims as they relate to biologic medicines will not be patentable.

Europe has an express directive that provides 'biological material which is isolated from its natural environment or produced by means of a technical process even if it previously occurred in nature'[2] is patentable subject matter.

2 European Patent Convention, EU Directive 98/44/EC, Article 52 and Regulation 27.

In the US, isolated and purified biologics that are essentially identical to their naturally occurring forms will generally not be eligible for patent protection. Patents previously granted for certain biologics may now be vulnerable to an invalidity attack. The relevant court decisions have been about innovations relating to diagnostic and treatment methods. However, they have clear reach into the biologic medicines space with potential impact on the availability of patent protection for inventions comprising drug screening, drug mechanisms of action, and diagnostic and treatment methods associated with biologics.

Until recently, the Australian position was widely assumed to be broadly permissive, and thought to extend to both methods of treatment of humans and diagnostic methods performed on a human, as well as isolated biological material even if it previously occurred in nature. The High Court's decision in *Myriad* in October 2015, which excluded Myriad's claims to 'isolated nucleic acids', has altered this. The case did not directly address biologic medicines – the claimed innovations relate to diagnostics. However, there is potential impact in the biologic medicines space. A further complication is that the court was only asked to consider claims to the 'isolated nucleic acids'. The full extent of the limitation remains unclear. For example, there is no guidance on whether methods using 'isolated nucleic acids' would be patentable. In addition, the approach to claims construction in *Myriad* could be applied to other aspects of biologic medicines, thereby broadening the scope of unpatentable subject matter.

Marketing authorisation barriers

In Europe, applications made to the central authority since 20 November 2005 have been granted eight years of data exclusivity and 10 years (extendable to 11 years in certain circumstances) of market exclusivity. The EU barriers are therefore sometimes referred to as '8+2+1'.

In the US, the potential imbalance between the investment required to make the advances offered by biologic medicine and the lack of patent protection is addressed by the provision of longer data exclusivity for biologic medicines and by providing a period of marketing exclusivity. As noted earlier, these can provide an effective monopoly of up to 12 years after marketing authorisation of the original biologic medicine was obtained. The US also provides specific statutory pathways for the registration of follow-on products, which address both patent protection and regulatory protection, including the data and marketing exclusivity period. These schemes are different depending on whether the original product is a small molecule drug or a biologic medicine.

By contrast, the current situation in Australia is no different from that with small molecule drugs – a narrow data exclusivity period of five years. While Australia purports to have provisions that link patent protection and marketing authorisation, these are unaffected by whether the product is a biologic. They have had very limited impact.

Reimbursement approval and interchangeability

There are also differences in the way that interchangeability operates. In Europe, the EMA specifically does not address interchangeability. This is considered to be an issue for national NRAs. In the US, it is a matter for the FDA and is part of the integrated pathway for the assessment of follow-on biologics. If a biosimilar product can demonstrate interchangeability, it can be entitled to a further period of market exclusivity of up to 42 months during which no other biosimilar product can be determined to be interchangeable.

In Australia, at least until recently, it was considered that this was a matter for the TGA and that the 'a-flagging' of biosimilar medicines would only occur if the TGA considered that there was evidence to support interchangeability. It is no longer clear that this is the case, with the statutory power now vested in the PBAC. Whether this will provide the benefits that should flow from access to biosimilars is far from clear.

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YOUR FEEDBACK

Please contact us if you would like to discuss the challenges and opportunities presented by biologics and biosimilars.

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