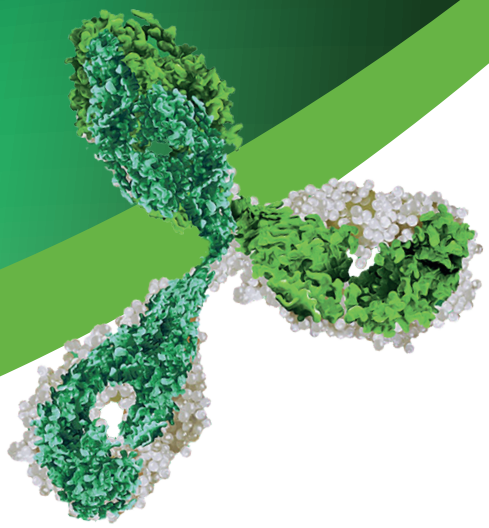
BIOSIMILAR MEDICINES IN AUSTRALIA



FACTSHEET

Track and Traceability, and Pharmacovigilance

Key points covered in this document

1. Medicine substitution - track and traceability
2. Quality management of prescription medicines
3. Pharmacovigilance around therapeutic products
4. Regulation of biological and biosimilar medicines

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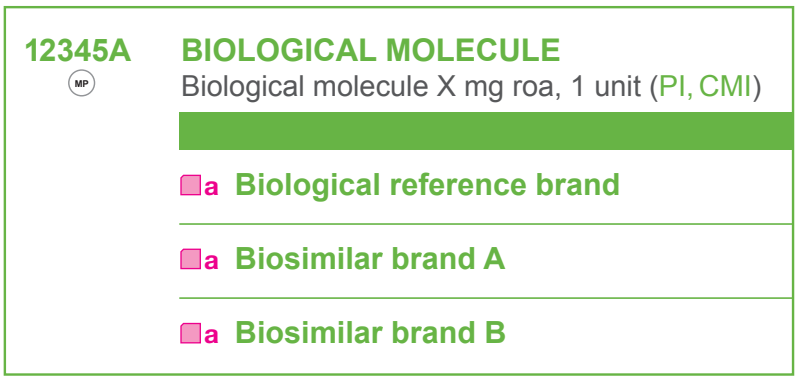
TRACK AND TRACEABILITY, AND PHARMACOVIGILANCE

Biological Medicines – Tracking & Traceability

Once approved for marketing by the TGA based on therapeutic equivalence to its reference biological medicine, each biosimilar brand of a medicine is assessed on a case-by-case basis by the **Pharmaceutical Benefits Advisory Committee (PBAC)** for reimbursement through the **Pharmaceutical Benefits Scheme (PBS).**[1]

If data are sufficient – including supportive switch data – the PBAC may recommend that a biosimilar medicine has **'brand equivalence'** to the reference biological medicine and may be substituted at the point of dispensing.[1–3]

Brands that can be substituted by the pharmacist are indicated in the Schedule of Pharmaceutical Benefits by an 'a-flag'. **Only 'a'-flagged medicines can be substituted by the pharmacist.** Note that there are no 'a' flags for brands of medicines on the *Efficient Funding of Chemotherapy'* Schedule, however they can be substituted under section 33(2) of the *National Health (Efficient Funding of Chemotherapy) Special Arrangement 2011.*[3]



Adaptation of PBS a-flagging, for illustrative purposes only.

The Pharmaceutical Society of Australia Professional Practice Standards states that brand substitution may only occur after **consultation with, and agreement from, the patient or carer.** Pharmacists should also consider the selection of brands for patients on long-term therapy to avoid confusion.[4]

Community-based doctors – in consultation with their patients – decide what medicine is prescribed. As with any prescription, if the 'Brand substitution not permitted' box is checked, a pharmacist must prescribe the nominated brand of medicine.

In the public hospital setting, brand decisions are made by clinician-led committees on behalf of doctors and patients. Decisions are made based on **safety, efficacy and cost-effectiveness** within the local health system. The Council of Australian Therapeutic Advisory Groups (CATAG) has published the following guidance on the use of biosimilar and biological medicines in hospitals:[5]

1. The governance of biological/biosimilar medicines within the hospital system should be no different to that of any other medicine.

2. The selection of a biological/biosimilar medicine as first-line therapy in treatment-naïve patients should be subject to evidence of **safety, efficacy and cost-effectiveness.**

3. Biological/biosimilar medicines should be prescribed by both the **active ingredient** name and the **trade name**.

4. A biological maybe interchangeable with its biosimilar/s at dispensing only where it has been determined to be substitutable by a Drug and Therapeutics Committee (DTC).

5. Patients should be **fully informed** when receiving treatment with a biological/biosimilar medicine.

6. Switching between a biological and its biosimilar medicine/s should be in accordance with a DTC–approved treatment protocol that includes a monitoring plan.

7. The selection of a biological/biosimilar medicine as second-line therapy should be in accordance with a treatment pathway approved by the Drug and Therapeutics Committee.

8. There should be a **patient-centred pharmacovigilance** framework within each hospital or health service to monitor and report outcomes and any adverse effects associated with biological/biosimilar medicine therapy.

9. The **active ingredient** and **trade name** of the biological/biosimilar medicine should be clearly communicated at all transitions of care.

TRACK AND TRACEABILITY, AND PHARMACOVIGILANCE

Quality Management of Prescription Medicines

In Australia, all prescription medicines are registered on the **Australian Register of Therapeutic Goods (ARTG)** and are regulated by the **Therapeutic Goods Administration (TGA)** to ensure that appropriate practices are followed throughout a product's entire lifecycle.[6–8]

TGA Overview

- The TGA is responsible for regulating medicines and medical devices;
- The TGA administers the Therapeutic Goods Act 1989, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of **quality**, **safety** and **efficacy**;
- The work of the TGA is based on applying **scientific and clinical expertise** to decision making, to ensure that the **benefits** to consumers outweigh any **risks** associated with the use of medicines and medical devices;
- The TGA relies on the **public**, **healthcare professionals** and **industry** to report problems with medicines or medical devices. The TGA investigates reports received by it to determine any necessary regulatory action.[9]

Before a prescription medicine can be marketed in Australia, all available data (chemical, non-clinical and clinical) is evaluated by experts in the relevant scientific and clinical fields. Following consideration, the TGA decides whether the **known benefits outweigh the potential risks** of the medicine and thus, whether the medicine should be registered for supply in Australia.[6]

Risk management plans consist of an overview of safety information and a plan of activities that will be undertaken to characterise and minimise risks associated with the medicine including:

- **Pharmacovigilance activities,** designed to investigate particular risks, or to fill gaps of knowledge, such as further studies or active monitoring for certain adverse events.
- **Risk minimisation activities,** such as educational materials and activities for health professionals and consumers, designed to reduce the potential for harm to patients.[6]

Since 2009, all new prescription medicines are required to have a risk management plan.[6]

All medicines on the ARTG must comply with relevant **Good Manufacturing Practice (GMP)** requirements as imposed under the *Therapeutics Goods Act 1989*. The TGA inspects manufacturing facilities to ensure compliance with GMP standards.[6]

The TGA actively monitors the safety of medicines marketed in Australia to contribute to a better understanding of their possible adverse effects when they are used **outside the controlled conditions of clinical trials.**[6]

Post-market safety monitoring by the TGA includes activities to identify and investigate safety signals; communication of this information to health professionals and the public; and appropriate regulatory action, such as suspending or cancelling registration, or narrowing the population in which the medicine can be used.[6]

The TGA has adopted a **risk management approach** to its pharmacovigilance activities, guided by the following principles:[10]

1. Communication of safety information to the public

2. Uphold product efficacy and safety standards

3. Adopt a product lifecycle approach
   - Capturing the entire body of evidence that accumulates through a product's lifecycle

4. Align with international best practices and standards

5. Facilitate industry compliance with vigilance best practices and monitoring
   - Provision of guidelines and monitoring to ensure adherence

6. Align with the TGA's decision-making framework
   - Ensuring transparency, timely decision-making and meaningful public involvement

7. Continuously improve therapeutic product vigilance
   - Vigilance requirements are subject to reconsideration based on the evolution of knowledge, technology, best practice standards and societal expectations

TRACK AND TRACEABILITY, AND PHARMACOVIGILANCE

Quality Management of Biological Medicines in Australia

Biological medicines are pharmaceutical products that contain one or more active substances that are **derived from living cells or organisms.** Biological medicines are defined as either the **'reference'** (the first registered brand), or **'biosimilar'** (a highly similar version of the reference product). This is in contrast with chemically synthesised small-molecule drugs where the generic is identical in its active ingredients to the reference product.[11,12]

Biological medicines are large, complex proteins made by living systems. The variable nature of these living systems leads to inherent variation in the molecules they produce. Such small-scale variation is considered a normal feature of any biological medicine, including the reference product, and is tightly controlled by the strict boundaries of manufacturing and regulatory processes.[11–13]

TGA regulations require that biological medicine manufacturers keep an **'in-house primary reference standard'** of the biological reference medicine for continual comparison with future batches.[14]

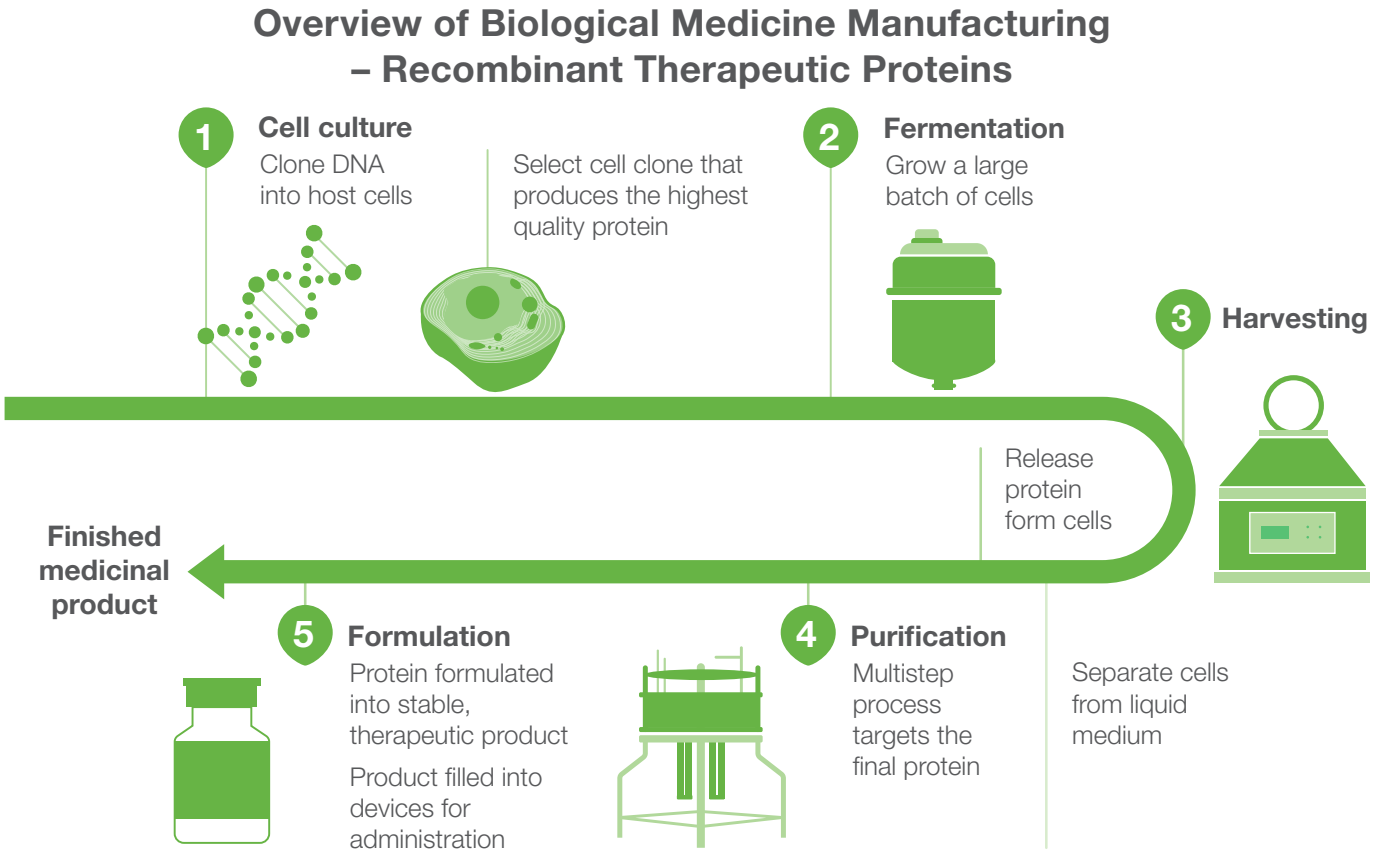


Figure adapted from IGBA. *The era of biological medicines.*[15]

Before a biosimilar medicine can be registered in Australia, comparability of **physiochemical**, **biological and immunological** characteristics, and clinical **efficacy and safety** to the reference biological medicine must be demonstrated through a number of laboratory and clinical stuides.[16]

All biological medicines (reference and biosimilar) are evaluated through the **same strict requirements** and guidelines as those for all prescription medicines. In addition, the TGA has adopted several European guidelines that outline the quality, nonclinical and clinical data requirements specific to biosimilar medicines; as well as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline on the assessment of comparability.[16]

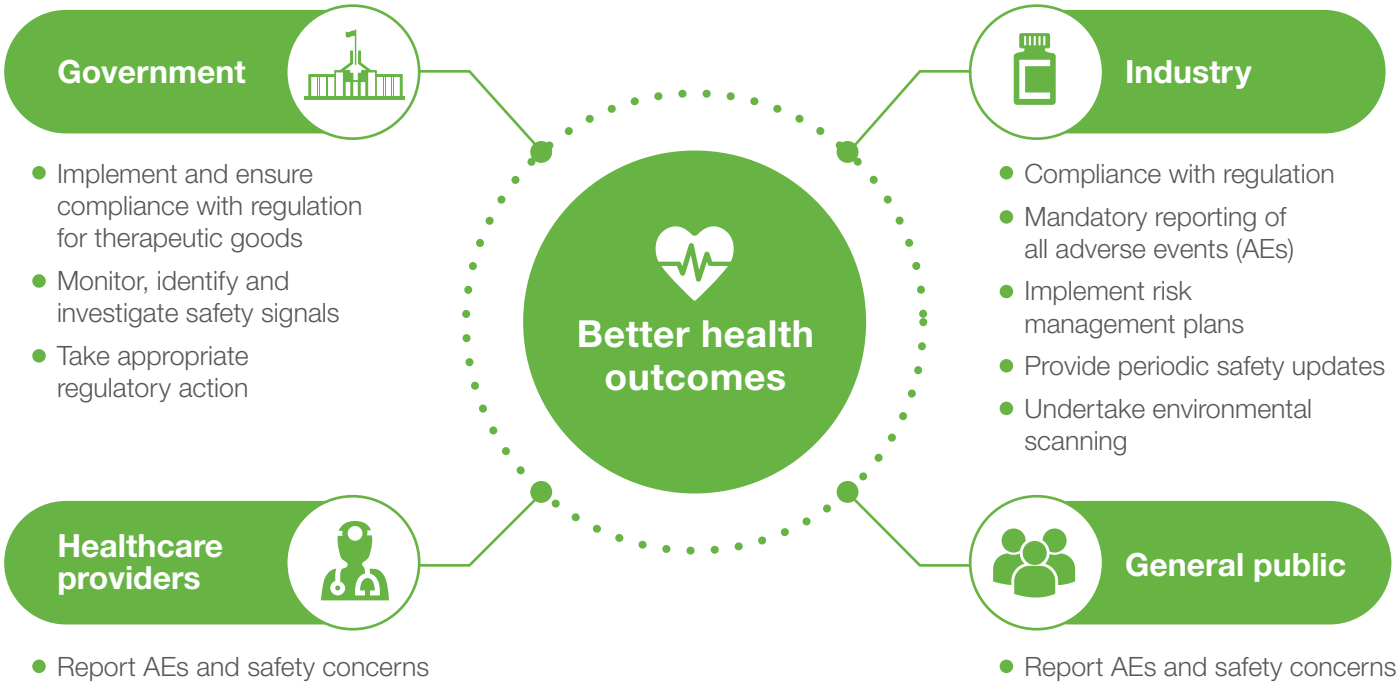
As with all prescription medicines, manufacturers of biological medicines must comply with:

- GMP requirements as imposed under the Therapeutics Goods Act 1989, in addition to requirements specific to biologicals *(Australian code of GMP for human blood and blood components, human tissues and human cellular therapy products)*[9,17]
- Post-registration pharmacovigilance requirements. This can include a **Risk Management Plan (RMP)** and **Periodic Safety Update Reports (PSURs)**.[10]

The regulatory conditions for biosimilar medicines in Australia mean that a biosimilar medicine approved for use in the Australian market can be said to have **no clinically meaningful differences** and be **therapeutically equivalent to its reference product.** Once approved, healthcare professionals and patients can expect similar health outcomes whether the biosimilar medicine or its reference medicine is used.[11]

Working Together for Better Health Outcomes

The National Medicines Policy is based on a partnership with Governments, health educators, health practitioners and other healthcare providers and suppliers, the medicines industry, consumers and the media to bring about better health outcomes for all Australians, focusing especially on people's access to, and appropriate use of, medicines.[6,18]



An International Overview of Biological Medicine Prescribing Regulations and Practices

Biosimilar medicines have the potential to generate substantial cost savings for the Australian healthcare system through increased market competition.[19] Successful market uptake of biosimilar medicines and subsequent cost saving is dependent on several factors, **including patient acceptance.** Policies such as automatic substitution, interchangeability designation, and encouraging switching to biosimilar medicines can help to **drive the uptake of biosimilar medicines** and **enhance confidence.**

A summary of global policies related to interchangeability, switching, substitution and prescribing of biosimilar medicines is provided in Table 1.[20]

Table 1. Summary of policies related to interchangeability, switching, substitution and prescribing[20]

	Countries where these policies exist
Policies related to interchangeability, switching, and substitution	
"Interchangeability" designation for a biosimilar medicine approved by the regulatory agency	• USA[a]
Market exclusivity (for a limited period) for the first interchangeable designated biosimilar medicine	• USA[a]
Automatic substitution allowed for biosimilar medicines Note: Some conditions may apply (e.g. automatic substitution may be prohibited by the physician) and policy may only apply to specific biosimilar medicines	• USA ("interchangeable" designated biosimilar medicine only) • Germany ("bioidentical" biosimilar medicine only) • France (for "treatment-naïve" patients only) • Australia ("a-flag" designated biosimilar medicine only)

		Countries where these policies exist
Policies related to interchangeability, switching, and substitution - cont'd		
Authorities recommend prescribing biosimilar medicines for treatment-naïve patients		• Germany • Norway • France • Netherlands • Australia
Switching is encouraged for patients already treated with a reference biological medicine (physician-led)		• Germany • France • Norway • Finland • Australia
Policies related to supplier		
Pricing policy	Free pricing	• US • UK (but subjected to PPRS rule)
Pricing policy	Price of reference drug and biosimilar medicines is the same	• Germany • Norway • Australia
	Direct price controls (e.g. mandatory discounts, on market entry, market competition)	• France • Norway (stepped price discount over time and increase in number of competitors) • Finland • Australia
Procurement policy	Tendering at hospital, regional, and national level	• UK • Germany • France • Norway • Netherlands

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		Countries where these policies exist
Policies related to supplier cont'd		
Procurement policy	Rebates	• Germany
	Quotas	• Germany (for SHI)
Prohibit or limit discounts offered to individual retail pharmacies	Prohibit or limit discounts offered to individual retail pharmacies	• Germany • France (restriction on level of discount offered) • Norway
	Price mark-up adjustments	• UK • Netherlands
	Clawback arrangements	• UK • Germany • Netherlands
Pharmacy policies	Regressive mark-up to encourage dispensing of lower-cost drugs	• France • Norway
	Pharmacists are allowed to keep the difference when dispensing medicine cheaper than the reimbursement price	• Australia

	Countries where these policies exist
Prescribing Incentives	
Monetary incentive for prescribing “best value” medicine	• USA • UK
Gain-sharing agreement	• UK • Germany
Pharmaceutical budget limit for clinics	• UK • Germany
Penalties for exceeding pharmaceutical budget limit	• Germany
Prescribing quotas and incentives for switching to biosimilar medicines for the prescriber or hospital	• Germany • France
Mandatory prescribing of tender-winning drugs or cheaper options	• Norway • Germany

Adapted from International policies on the appropriate use of biosimilar drugs. Ottawa: CADTH; 2018.
[a]As of September 2018, none of the biosimilar medicines approved by the FDA have received an interchangeable designation.

Switching refers to a prescriber deciding to substitute one medicine with another with the same therapeutic intent.

Interchangeability refers to two or more medical treatments that are therapeutically equivalent and can be safely substituted in clinical practice. If two or more medicines are considered interchangeable, the prescriber may choose to prescribe either of the medicines for a patient to treat the same condition. This generally occurs between two different medicines, rather than between brands or biosimilars of the same medicine. This may be governed by regulatory agencies.

Substitution is a practice of replacing one drug for another at the pharmacy level, after the prescriber has written a prescription. Automatic substitution refers to replacing one drug with another at the pharmacy level, without consulting the prescribers.

Supply side policies refer to policies implemented by payers, and policies related to pricing and procurement. Prescribing quotas and targets may be implemented to encourage prescribing of a specific group of drugs.

AE, adverse events; **ARTG,** Australian Register of Therapeutic Goods; **CATAG,** Council of Australian Therapeutic Advisory Groups; **GMP,** Good Manufacturing Practice; **ICH,** The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; **IGBA,** International Generic and Biosimilar Medicines Association; **PBAC,** Pharmaceutical Benefits Advisory Committee; **PBS,** Pharmaceutical Benefits Scheme; **PPRS,** Pharmaceutical Price Regulation Scheme; **PSUR,** Periodic Safety Update Reports; **RMP,** Risk Management Plan; **SHI,** Statutory Health Insurance; **TGA,** Therapeutic Goods Administration.

References

1. Pharmaceutical Benefits Advisory Committee. Public Summary Document – March 2018 PBAC Meeting. 11.04 Considering brand equivalence/ substitution for biosimilar medicines.
2. Australian Government – Department of Health. Biosimilar Uptake Drivers. Available at: http://www.pbs.gov.au/info/general/biosimilars. Accessed 1 October 2018.
3. NPS Medicinewise – RADAR: Brand equivalence – 'a' flagging explained. 1 August 2013. Updated 15 Match 2017. Available at: https://www.nps.org.au/radar/articles/brand-equivalence-a-flagging-explained. Accessed October 2018.
4. Pharmaceutical Society of Australia. *Professional Practice Standards.* Version 5. 2017. Available at: https://www.psa.org.au/practice-support-industry/professional-practice-standards/. Accessed August 2019.
5. Council of Australian Therapeutic Advisory Groups. *Overseeing Biosimilar Use.* V2, September 2016. Available at: http://www.catag.org.au/wp-content/uploads/2012/08/OKA10798-CATAG-Overseeing-biosimilar-use-Version-2-final.pdf. Accessed August 2019.
6. Australian Government – Department of Health. TGA. *Evaluation of a new medicine - The TGA's lifecycle approach to regulation.* 30 June 2011. Available at: https://www.tga.gov.au/behind-news/evaluation-new-medicine-tgas-lifecycle-approach-regulation. Accessed August 2019.
7. Australian Government – Department of Health. TGA. *Australian Regulatory Guidelines for Prescription Medicines (ARGPM).* Available at: https://www.tga.gov.au/publication/australian-regulatory-guidelines-prescription-medicines-argpm. Accessed August 2019.
8. Australian Government – Department of Health. TGA. *Medicines and TGA classifications.* Available at: https://www.tga.gov.au/medicines-and-tga-classifications. Accessed August 2019.
9. Australian Government – Department of Health. TGA. *Australian Code of Good Manufacturing Practice for human blood and blood components, human tissues and human cellular therapy products.* V1.0, April 2013. Available at: https://www.tga.gov.au/sites/default/files/manuf-cgmp-human-blood-tissues-2013.pdf. Accessed August 2019.
10. Australian Government – Department of Health. TGA. Therapeutic product vigilance v1.4 September 2019. Available at https://www.tga.gov.au/publication/therapeutic-product-vigilance. Accessed July 2019.
11. Australian Government – Department of Health. *Biosimilar medicines: the basics for health care professionals.* P11756. Updated: March 2017. Available at: http://www.health.gov.au/internet/main/publishing.nsf/content/ biosimilar -awareness-initiative/$File/Biosimilar-medicines-the-basics-for-healthcare-professionals-brochure.pdf. Accessed August 2018.
12. Dörner T, Strand V, Castañeda-Hernández G, *et al. Ann Rheum Dis.* 2013;72(3):322-8.
13. Schneider CK. *Ann Rheum Dis.* 2013;72(3):315-8.
14. Australian Government – Department of Health. *Biosimilar medicines regulation V2.2.* Updated: April 2018. Available at: https://www.tga.gov.au/sites/default/files/biosimilar-medicines-regulation.pdf. Accessed September 2019.
15. International Generic and Biosimilar Medicines Association (IGBA). *Chapter 1. The era of biological medicines.* Available at: http://www.igbamedicines.org/doc/Module1.pdf. Accessed August 2019.
16. Australian Government – Department of Health. TGA. *Regulation of biosimilar medicines. V2.2,* April 2018. Available at: https://www.tga.gov.au/publication/biosimilar-medicines-regulation. Accessed August 2019.
17. Australian Government – Department of Health. TGA. *Manufacturing biologicals.* Available at: https://www.tga.gov.au/manufacturing-biologicals. Accessed August 2019.
18. Australian Government – Department of Health. *National Medicines Policy Document.* 04 June 2014. Available at: https://www1.health.gov.au/internet/main/publishing.nsf/Content/national-medicines-policy. Accessed August 2019.
19. Australian Government – Department of Health. Biosimilar Uptake Drivers. Available at: http://www.pbs.gov.au/info/general/biosimilars. Accessed August 2019.
20. International policies on the appropriate use of biosimilar drugs. Ottawa: CADTH; 2018. (Environmental scan; no. 80).

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