

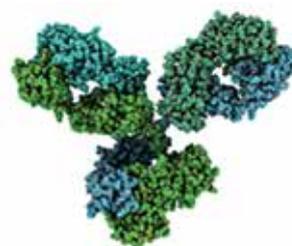
BIOSIMILAR MEDICINES

INFORMATION FOR PRESCRIBERS

Biological medicines are pharmaceutical products that contain one or more active substances that are derived from living cells or organisms.¹

A biosimilar medicine is a highly similar version of an already registered biological medicine (the reference biological medicine).¹ This is in contrast to small-molecule drugs, produced by chemical synthesis, where the generic product is identical to the reference medicine.²

Biological medicines are generally larger and more complex than chemically synthesised medicines



Chemically synthesised medicine

Type of molecule Small molecule

Synthesis Chemical

Uniformity Single substance

Size 21 atoms (aspirin)

Growth hormone

Protein (without sugars)

Bacterial

Single main substance

3000 atoms (HGH)

Antibody

Glycoprotein (variable sugars)

Mammalian

Mixture of variants

>20,000 atoms (mAb)

The complexity of biological medicines is such that they cannot usually be synthesised by conventional methods

Abbreviations: HGH, human growth hormone; mAb, monoclonal antibody.

Adapted from International Alliance of Patients' Organizations. Briefing paper on Biological and Biosimilar Medicines 2013. Available at: <http://bit.ly/2qZm7N1>. Accessed July 2017.³

As 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, known as 'microheterogeneity'. Batches of the same biological medicine can also demonstrate minor differences, a phenomenon known as 'batch-to-batch variation'.^{1,2,4} Such small-scale variation is considered a 'normal' feature of any biological medicine and is tightly controlled by the strict boundaries of manufacturing and regulatory processes.^{1,2,4}

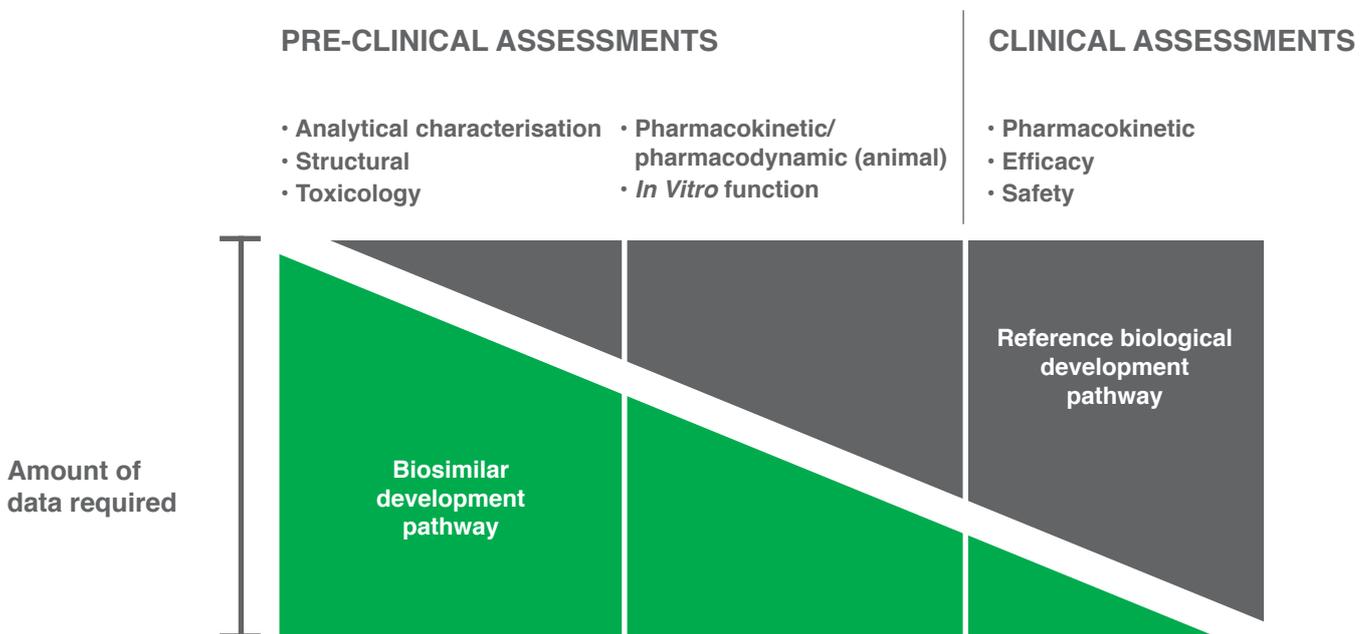
As biosimilar medicines are designed and engineered using the latest technology to resemble their reference product as closely as possible, demonstrating high similarity is at the foundation of biosimilar medicine development.⁵ All critical quality attributes (i.e. those impacting the function of the molecule) have been carefully evaluated to **demonstrate no clinically meaningful differences**.¹

Development of biosimilar medicines

The complex nature of biological medicines means a more rigorous comparability exercise of a biosimilar to its reference biological is warranted than for generics of small-molecule drugs.^{1,2,4-7}

Biosimilar medicines are approved on the totality of evidence gathered through a stepwise approach of comprehensive preclinical assessments and a tailored clinical program to confirm there are **no differences in clinical efficacy, safety or immunogenicity between the biosimilar and its reference product**. This contrasts with the reference biological medicine development, where the focus is on establishing the clinical benefit of the medicine.

Comparison of the development pathway of reference biological vs biosimilar medicines



Adapted from Bui LA *et al.* Key considerations in the preclinical development of biosimilars. *Drug Discovery Today* 2015; 20(Suppl 1): 3–15.⁸

1 Define and characterise the reference product

2 Complete manufacturing process development of the biosimilar medicine

3 Confirm comparability between the biosimilar medicine and the reference product

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 to be **therapeutically equivalent** to its reference product.^{1,6}

Contributing to a sustainable healthcare system

Biosimilar medicines can have lower development costs compared to their reference product as they can undergo a more streamlined clinical trial program.⁹⁻¹¹ Whilst price reductions for biological medicines may not be as large as those seen with small-molecule drugs and their generics,^{5,10,12} competition between brands could still generate significant savings for the Australian Pharmaceutical Benefits Scheme (PBS).^{5,9,12}

In Australia, a **statutory price reduction of 25%** applies to all brands of a medicine once the first generic or biosimilar version is listed on the PBS.¹³

In addition to the statutory price reduction, price disclosure arrangements mandated by the PBS ensure that prices for brands more closely reflect the prices in the market and encourage market competition. Where discounting is occurring due to competition, price disclosure reduces prices progressively over time, providing better value for money to the Australian taxpayer.¹³⁻¹⁵

Savings made from biosimilar medicines use could be reinvested into other areas of the Australian healthcare system such as expanded access of existing biological medicines or funding new healthcare treatments.^{1,13}

Biosimilar medicines in practice

A physician may choose to prescribe a biosimilar medicine in one of three scenarios:^{2,16-18}

- When **initiating** a patient onto their first biological medicine, and there is an approved biosimilar of the chosen medicine available,
- When **changing** therapeutic molecules due to loss of response or poor tolerability, for example, to an alternative molecule for which a biosimilar medicine is available,
- Proactively **switching** from a reference biological medicine to its biosimilar, or between biosimilar brands of the same molecule while treatment with that molecule continues to be successful.

Switching to a biosimilar medicine is a choice that can be expected to offer a comparable clinical result to prescribing the reference brand, while potentially reducing expenditure and, therefore, assisting in the sustainability of the healthcare system.¹

Uptake drivers for biosimilars

To support the uptake of biosimilar medicines in Australia, the Australian Government has introduced ‘uptake drivers’ that may be applied to specific biosimilar brands on a case-by-case basis following recommendations by the PBAC:¹³

- 1. Encouragement to prescribe a biosimilar medicine in biological medicine-naïve patients:** While biosimilar medicines are available to all patients, an administrative note will be added in the Schedule of Pharmaceutical Benefits for affected biological medicines that *“Prescribing of biosimilar brand(s)... is encouraged for treatment-naïve patients. Encouraging biosimilar prescribing for treatment-naïve patients is Government policy. A viable biosimilar market is expected to result in reduced costs for biological medicines, allowing the Government to reinvest in new treatments.”*¹³
- 2. A simpler and faster approval process for prescribing biosimilar brands:** Reference biological medicines will retain their existing authority requirement, while biosimilar medicine brands may be reviewed to have a lower-level authority requirement; for example, a written authority versus a streamlined authority, respectively.¹³

These drivers remain underpinned by key principles, such as the prescribing physician and patient having the final decision regarding the selection of biological medicine.¹³

Visit this Pharmaceutical Benefits Scheme (PBS) webpage <https://www.pbs.gov.au/info/general/biosimilars> for more information about the Australian Government’s biosimilar uptake drivers.

Brand equivalence

Once approved for marketing by the Therapeutic Goods Administration (TGA) based on therapeutic equivalence to its reference biological medicine,^{6,19} 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 PBS.

As part of this assessment and if data are sufficient, 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.^{1,19,20}

If approved as such, the PBS listings for those brands of biological medicines are given an ‘a’ flag (see example below), allowing for brand substitution at the pharmacy level following consultation with, and acceptance by, the patient.^{1,18,19}

| | |
|-------------------------------------------------------------------------------------|------------------------------------------------|
| 12345A | BIOLOGICAL MOLECULE |
|  | Biological molecule X mg roa, 1 unit (PI, CMI) |
|  | Biological reference brand |
|  | Biosimilar brand A |
|  | Biosimilar brand B |

An ‘a’ flag provides prescribers with the assurance that there are no clinically meaningful differences in the critical and quality attributes that affect safety, effectiveness or quality between the reference and biosimilar medicine.

Pharmacovigilance of biological and biosimilar medicines

As part of a biosimilar medicines application for approval in Australia, as well as in Europe and the USA, the manufacturer may be required to submit a Risk Management Plan (RMP).^{2,6,21-23} A RMP is tailored for the individual product based on experience gained with the reference biological medicine.^{6,21} These RMPs can include post-approval clinical trials and enrolment of patients in biological medicine registries.^{21,24}

As with all TGA-approved therapies, biosimilar medicines must comply with post-registration pharmacovigilance requirements. This can include a Risk Management Plan (RMP) and Periodic Safety Update Reports (PSURs).^{1,6,25}

These processes ensure safety, effectiveness and immunogenicity characteristics of biosimilar medicines are monitored long after market approval, perpetually expanding data and understanding, including how they compare to their originator products.^{1,2}

The TGA monitors marketed medicines closely, and all stakeholders should report adverse events to the TGA.^{1,22,25}

Clinical experience with biosimilar medicines

- The first biosimilar medicine was approved for use in Europe in 2006, meaning we have **over a decade of clinical experience with biosimilar medicines available**, and more than 700 million patient-days of experience with biosimilar medicines in Europe alone.^{2,26,27}
- The first biosimilar medicine was approved in Australia in 2010¹
- In 2018, a systematic review of 90 studies assessing the efficacy and safety of switching from a reference biological medicine to its biosimilar medicine concluded that there were **no immunogenicity-related safety concerns nor diminished efficacy**.²⁶

Further information

Watch the video talk series with specialists and pharmacists to hear their insights and experiences with biosimilar medicines



Consumer/carer materials are available on the Biosimilar Hub to help support the conversation about biosimilar medicines with patients. Materials are freely available to download or print at biosimilarhub.com.au/resources/

Further information for healthcare professionals is available at www.biosimilarhub.com.au

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