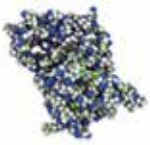
BIOSIMILAR MEDICINES | INFORMATION FOR PHARMACISTS

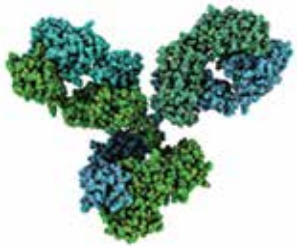
What are biological and biosimilar medicines?

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 with 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	Biological medicine - growth hormone	Biological medicine - monoclonal antibody
Type of molecule	Small molecule	Protein (without sugars)	Glycoprotein (variable sugars)
Synthesis	Chemical	Bacterial	Mammalian
Uniformity	Single substance	Single main substance	Mixture of variants
Size	21 atoms (aspirin)	3000 atoms (HGH)	>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]

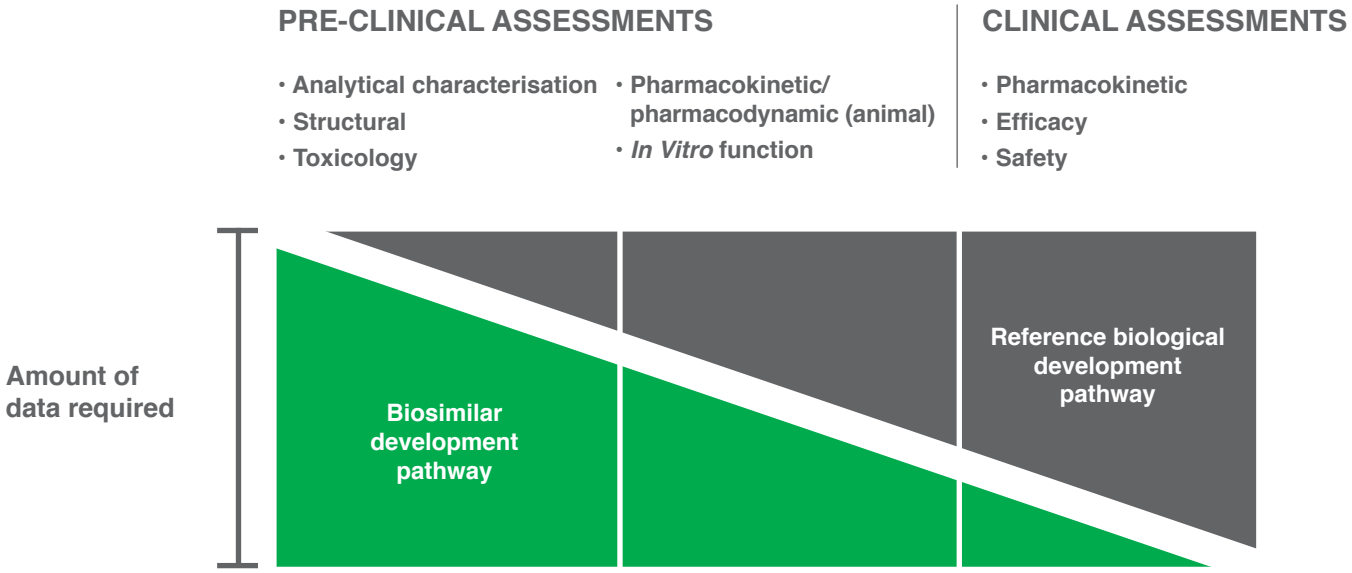
As biosimilar medicines are designed and engineered using the latest technology to resemble their reference product as closely as possible, demonstrating high similarity is at the foundation of biosimilar medicine development.[5] All critical quality attributes (i.e. those impacting the function of the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

How are biosimilar medicines developed?

The complex nature of biological medicines means a more rigorous comparability exercise of a biosimilar medicine 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 medicine and its reference biological. 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 I): 3–15.[8]

Stepwise comparability exercises ensure there are no clinically meaningful differences between the biosimilar medicine and the reference biological

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]

Biosimilar medicines contribute 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]

Regulation of biosimilar medicines in Australia

Regulatory requirements 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. Once approved, healthcare professionals and patients can expect similar health outcomes whether the biosimilar medicine or its reference product is used.[1,6]

PBS and PBAC

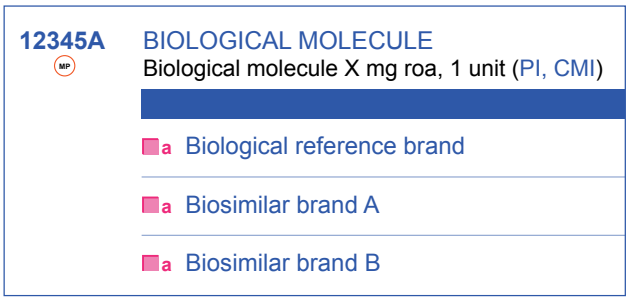
Once approved for marketing by the TGA based on therapeutic equivalence to its reference biological medicine,[6,16] each biosimilar brand of a medicine is assessed on a case-by-case basis by the Pharmaceutical Benefits Advisory Committee (PBAC) for reimbursement through the PBS.

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 point of dispensing.[1,16,17]

With regards to biosimilar medicines, the PBAC will make a case-by-case decision whether to recommend the **granting of an 'a' flag**, based upon:

- The TGA determining that the product is a biosimilar of the reference medicine as evidenced by Australian Register of Therapeutic Goods (ARTG) registration documentation;
- Availability of supportive data relating to the effects of switching between the reference product and the biosimilar product/s; and
- Practical considerations relating to substitution by the pharmacist at the point of dispensing. This includes strength of formulation, number of units per pack and maximum quantities between the brands, which may make substitution at the pharmacy level difficult from a practical perspective.[17]

If approved as such, the PBS listings for those brands of biological medicines are given an 'a' flag (see example below)



Biosimilar medicines in practice

An 'a' flag allows brand substitution at the pharmacy level following consultation with, and acceptance by, the patient.[1,16,18]

'a' flagging enables pharmacists to substitute between the reference biological and a biosimilar medicine without consulting the prescriber. This can only occur if:

- the 'Brand substitution not permitted' box on the prescription has NOT been checked; AND
- the patient or carer has been consulted and agrees.

Professional Practice Standards[19]

The pharmacist ensures that all dispensed and supplied therapeutic goods and associated pharmacy services reflect the prescriber's intentions, and are consistent with the quality use of medicines and the patient's health goals and values.

When substituting brands of biological medicines, pharmacists must:

- Ensure the patient fully understands the nature of substitution and has adequate opportunity to contribute to the decision before it occurs
- Confirm that the 'Brand substitution not permitted' has not been selected by the prescriber on the original prescription before offering substitution to the patient

Discussing and educating a patient on the brand they have been prescribed/dispensed can further support the quality use of medicines, especially if dispensed in the community setting. Patients can also keep or photograph their biological medicines packaging to enable its brand and batch number to be recorded at future healthcare interactions.[19,20]

Hospital pharmacists

In the public hospital setting, brand decisions are made by clinician-led committees and are based on the safety, efficacy and cost-effectiveness of the medicine.[1,21]

For more information, refer to the guiding principles from the Council of Australian Therapeutic Advisory Groups on the governance of biological and biosimilar medicines in Australian hospitals (www.catag.org.au/resources/#guidance).[21]

Commonly asked questions about biological and biosimilar medicines

Q. How much do we know about the way biosimilar medicines behave in the real world?

A. 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.[2,22,23]

Q. How much biosimilar medicine experience do we have in Australia?

A. The first biosimilar medicine was approved in Australia in 2010.[1]

Currently, there are 10 biological medicines which have at least one biosimilar medicine approved for use in Australia. These medicines are being used to treat serious conditions such as cancer, rheumatoid arthritis and inflammatory bowel diseases.

Q. What are the safety and efficacy implications of switching from a reference biological to a biosimilar medicine?

A. 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.**[22]

In addition, published international post-market research has found no difference in the safety or health outcomes of patients who switched to biosimilar medicines and those who remained on the reference biological medicine.[1,2,18,24]

Further information

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

The *'Biosimilar medicines: the essentials for consumers and carers'* leaflet is available to facilitate the conversation about biosimilar medicines with patients. Print or view online at: **biosimilarhub.com.au**.

Detailed information for healthcare professionals is available at the Biosimilar Hub **www.biosimilarhub.com.au**, your source of information, interviews and insights into the world of biosimilar medicines.

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