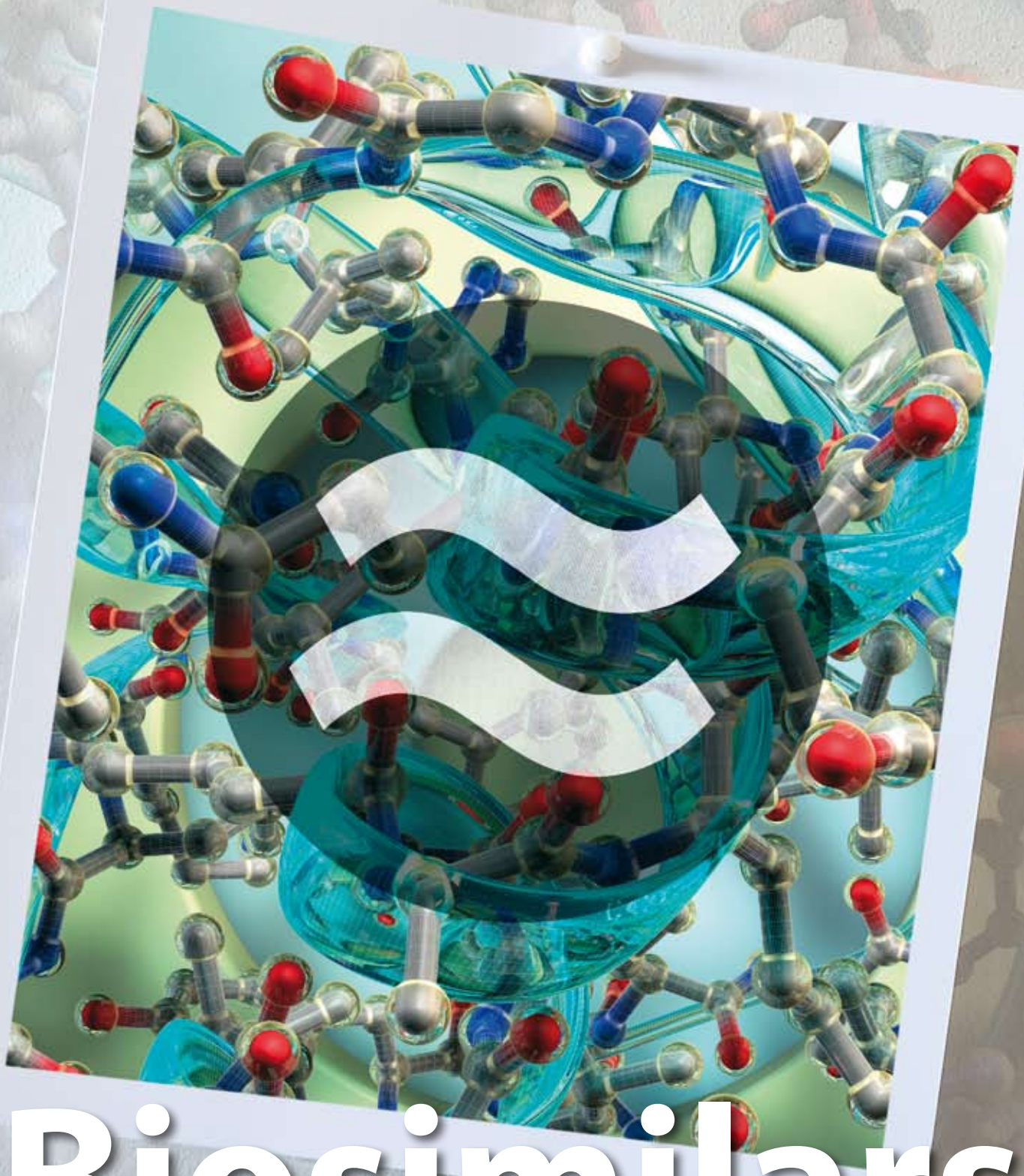


Biosimilars

– what does a primary care clinician need to know?

"Biosimilars" is likely to become an increasingly familiar term for clinicians in New Zealand and worldwide. Medicines produced from biological sources (biologics) have come to play a large role in clinical practice over the last few decades, including human hormones (e.g. human insulins) and monoclonal antibodies (e.g. adalimumab [Humira] and trastuzumab [Herceptin]) made with recombinant DNA technologies. Biosimilars are comparable versions of an existing biological medicine and can receive marketing approval once patent protection has expired for the innovator (original) biological medicine. Biologics and biosimilars are most likely to be initiated in secondary care, but primary care clinicians may find it useful to have some background knowledge of biosimilars in order to provide optimal care for patients using these medicines.

Biological medicines (also known as "biologics") are produced from living sources such as yeast, bacteria or animals, usually by genetic engineering; as opposed to pharmaceutical medicines which are chemically synthesised (including those initially derived from a plant source). The manufacture of biologics such as human insulin and erythropoietin only became possible when recombinant DNA technologies were introduced in the 1970–80s; these proteins are too complex to be manufactured by purely chemical processes.[1] The chemical composition of a biological medicine varies and includes products made of sugars, proteins or nucleic acids (DNA or RNA segments) alone or in combination.[2]

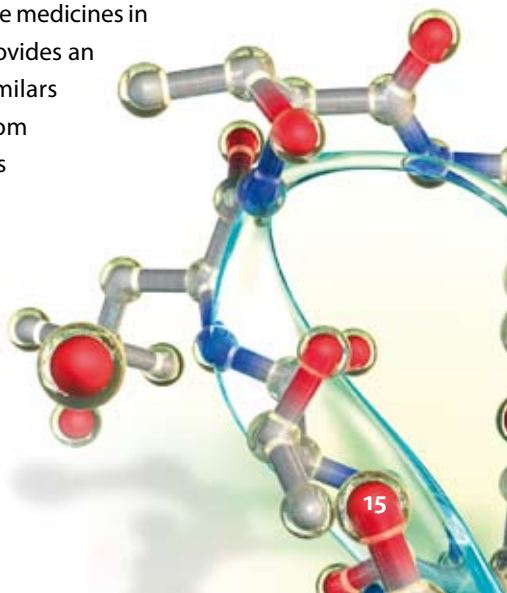
Most biologics currently in use are either monoclonal antibodies or proteins manufactured using genetically engineered bacteria or yeast cells, including:

- A variety of recombinant human hormones, cytokines and growth factors, e.g. erythropoietin, insulin, granulocyte colony-stimulating factor (G-CSF), human growth hormone
- Monoclonal antibodies designed to target specific proteins in the human body (the "mabs"), such as trastuzumab (Herceptin) which binds to the HER2 receptor, and adalimumab (Humira) which inhibits tumour necrosis factor alpha (TNFα)
- Fusion proteins such as etanercept, where the extracellular domain of a TNFα receptor is fused to part of a human IgG protein
- Antibody + drug combinations such as trastuzumab + emtansine (Kadcyla) in which the trastuzumab antibody is bound to a cytotoxic small molecule to deliver the drug to target cells

Biologics have become particularly important for the treatment of diseases characterised by inflammatory and immune changes, such as rheumatoid arthritis, Crohn's disease and multiple sclerosis, as well as treatments for patients with cancer. The high cost and increasing use of biological medicines means that they have become one of the largest and fastest growing areas of pharmaceutical expenditure in many countries, including New Zealand.[3]

Biosimilars are biological medicines that are designed to be comparable to an existing, approved, reference biological medicine once patent protection has expired on the original product; in much the same way as generics are off-patent versions of an existing chemically synthesised medicine.

The majority of biologics in use in New Zealand require prescription and Special Authority applications to be made by a relevant clinician in secondary care and this will remain the case in the near future. Therefore, general practitioners are unlikely to initiate the use of biological or biosimilar medicines. However, since more patients in New Zealand are likely to be using these medicines in the future, this article provides an overview of what biosimilars are, how they differ from generic pharmaceuticals and discusses areas of clinical certainty or uncertainty that are useful for the primary care team to be aware of.



Biosimilars: the new generics, but different

Biologics are typically larger and more structurally complex than chemically synthesised medicines; e.g. a monoclonal antibody can be approximately 800 times the size of an aspirin molecule.[4]

The production of biological medicines is different to the manufacture of a chemically synthesised medicine. For example, the production of a human hormone as a biological medicine requires:[1]

1. Genetic modification of a cell line so that it possesses the human hormone gene sequence
2. Cell culture, allowing cells to transcribe the DNA sequence, translate it into an amino acid sequence, and fold the amino acid chain into a three-dimensional protein
3. After protein translation, other modifications may include glycosylation of amino acids or cleaving of a portion of the amino acid sequence so that a prohormone is processed into an active hormone
4. Manufacturing steps to separate the hormone from the cells which produced it, and purify and concentrate the hormone for packaging into a formulation suitable for patient administration; currently almost all biologics in use worldwide are administered via injection

Generics can be made to have the exact same active ingredient, biosimilars cannot

Generic pharmaceutical medicines can usually be chemically synthesised to have the exact same molecular structure as the original patented pharmaceutical.[5] This is not the case for biosimilar medicines. The processes used to manufacture innovator biologics or biosimilars use living systems and are inherently variable. These medicines exhibit what is known as "microheterogeneity", where small differences in the protein or antibody may be detectable between batches of the same biologic produced by one manufacturer.[1] For example, a protein could have the same amino acid sequence but have differences in glycosylation patterns.[1] In addition, once an original biological medicine has come off patent, it is unlikely that a competing manufacturer will be able to exactly replicate the full manufacturing and production process of the innovator, especially as some aspects of the process may not be available in the public domain.

As a result of this complexity, no two batches of an original biologic medicine are identical, and similarly alternative versions of a biologic medicine **cannot be identical to the original; hence the name "biosimilars".**[1, 5] These medicines are also referred to as subsequent entry biologics, follow-on biologics, or similar biotherapeutic products.

Evaluating and approving biosimilars: a new challenge in medicine requires a new approach

The regulatory approval of generically equivalent medicines is dependent on demonstrating that the generic has an identical chemical structure and pharmacokinetic bioequivalence via the same route of administration in healthy volunteers as the original patented medicine.[5] Clinical trials to demonstrate that the generic medicine has equivalent clinical efficacy and safety as the innovator medicine are not required.

Due to variability in biosimilars, criteria for regulating generic medicines are insufficient to ensure that a biosimilar has the same clinical efficacy and safety as a previously patented biologic medicine.[5] In addition, since biologics can be large and structurally complex, it is difficult to analyse whether they have the same physical and chemical structure as the innovator biologic.[1]

This leads to the key questions which regulatory authorities face regarding the evaluation and approval of biosimilars:

- How much change can there be in a biosimilar, relative to the original biologic, before clinical efficacy and safety are affected?
- What is the best way to ascertain potential differences and evaluate the efficacy and safety of biosimilars?

Biosimilars are a relatively new area of medical science, and new regulatory frameworks for how to best answer these questions have been required and come into use over the last decade. In 2015, new guidelines on the approval of biosimilars from the Europe Medicines Agency and guidance from the Food and Drug Administration (FDA) to manufacturers in the United States have been released.[6–8] Increased market competition from off-patent biologic medicines has the potential to reduce costs and widen access so more patients can use them, which could be a desirable outcome; the challenge is to ensure that this can happen without compromising patient safety or reducing efficacy.

To address the question of how much difference there can be between a biosimilar and the originator biologic before clinical efficacy and safety are affected, many regulatory agencies around the world have devised processes for evaluating and approving biosimilars. In New Zealand, Medsafe has adopted the guidelines of the European Medicines Agency

for the approval of biosimilars.[9] These guidelines require the manufacturer of a biosimilar product to demonstrate that the biosimilar:[10]

A. Is similar to the reference medicine in terms of chemical and physical properties (the already approved, "original" biological medicine)

This is assessed by a range of laboratory experiments, such as antigen binding tests for antibodies. In general, there is no "gold standard" to quantify chemical and physical similarity; the purpose of these tests is to identify any differences between the biosimilar and the original biologic.

B. Does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy

This is assessed by a variety of tests including pharmacodynamic and pharmacokinetic studies, as well as clinical trials of efficacy compared to the reference biologic. These tests must demonstrate that any detected differences in chemical or physical properties do not have a meaningful impact on clinical efficacy and safety.[6] For example, biosimilar versions of epoetins are known to have different glycosylation profiles, but have been demonstrated to have the same clinical efficacy and safety, so are approved for use.[1] In the assessment of a biosimilar version of recombinant human follicle stimulating hormone (Ovaleap), the European Medicines Agency noted minor chemical differences are present compared to the innovator biologic (Gonal-f), but approved the biosimilar on the basis of clinical evidence of similar efficacy and safety.[11]

The European Medicines Agency has additional specific criteria depending on the type of biologic medicine under consideration, e.g. chemical and clinical efficacy criteria for biosimilar insulins, epoetins and filgrastims.[12, 13]

Are there any safety or efficacy issues with biosimilar medicines?

Multiple indications

A biological medicine may be used to treat patients with different conditions and be approved for multiple indications. The question which then arises is whether a biosimilar needs to be assessed in clinical trials for every indication of the original biologic, or could it be approved for all of the indications held by the original biologic medicine once similar efficacy and safety is shown for a subset of those indications?

When a biosimilar is approved for an indication which has not been directly assessed in clinical trials, regulatory agencies refer to these as "extrapolated indications". Authorities, including the World Health Organisation (WHO) and European Medicines Agency, have provided guidance on the scenarios that would form a sound scientific basis for approving a biosimilar for extrapolated indications, such as when a medicine is believed to have similar mechanisms of action in different conditions and is used in similar doses or durations.[7, 14] However, the interpretation of evidence can differ between regulatory authorities, e.g. a biosimilar version of Remicade (infliximab) is approved for a more limited range of indications in Canada than in most other countries.[15]

Extrapolated indications are likely to be an area of ongoing debate where there may be disagreements between regulatory authorities or clinicians depending on the biosimilar and indications in question.[14] Ultimately, for any medicine, safety and efficacy can only be demonstrated through the accumulated evidence of appropriate clinical trials and real world data on rates of clinical response and adverse effects.

Immunogenicity and tolerance

One of the key concerns with biologics and biosimilars is the potential for unforeseen adverse effects resulting from variability, especially immune reactions. The immunogenicity of biological products is likely to arise from their biological complexity but predicting whether a biological product will produce an immune reaction is difficult.[1, 7] The potential clinical impact of an immune reaction can also be highly variable; consequences can range from little clinical impact, to influencing the achieved dose and efficacy of the medicine or leading to the development of antibodies which cause autoimmune reactions.[14] As is the case with any new medicine, long-term data on the safety of biosimilars in large numbers of patients will not be available until these have been in clinical use for some time.

The lesson from Eprex

An example of an unforeseen adverse effect from a biological medicine comes from changes in the manufacture and use of the innovator biologic Eprex (epoetin alfa, a recombinant erythropoietin). Until the late 1990s bovine serum albumin (sourced from cows) was used as a vehicle in Eprex production. Due to concerns about the potential development of Creutzfeldt–Jakob disease, bovine serum albumin was swapped for another compound, polysorbate-80. Adverse reaction monitoring detected an increased occurrence of a rare condition in patients treated with Eprex: pure red-cell aplasia due to the presence of anti-erythropoietin antibodies. Subsequent investigation implicated the change

in vehicle as a cause of increased immunogenicity leading to the development of anti-erythropoietin antibodies in some patients. Other factors also implicated in the increased occurrence of pure red-cell aplasia included a change in clinical practice with increasing subcutaneous instead of intravenous administration, variable storage conditions and possible leaching of compounds from rubber stoppers in syringes.[16, 17]

This case involved a change in manufacturing process and administration of the original patented medicine, rather than the introduction of a biosimilar. However, it highlights that small alterations in the preparation of biologics could have important clinical effects, and this has informed current approaches to the safety of biologics and biosimilars. Firstly, changes in the manufacturing process of approved biologics are now more tightly regulated.[16] Secondly, it is recognised that biosimilars could have important differences in clinical effect even if they have little difference in terms of composition to the original biologic; thus, clinical tests of efficacy and immunogenicity in sensitive populations are included in current approval guidelines around the world.

Immunogenicity in European guidelines

The approval process for biosimilars in Europe requires that a manufacturer demonstrates comparable (or lower) immunogenicity to the reference product. For any medicines which are used long-term, the European Medicines Agency has stated that immunogenicity data for one year of use will normally be required for approval.[7] One of the concerns with extrapolated indications is that use in different patient populations (such as people with different autoimmune conditions) could influence immunogenicity.[14] The FDA and WHO recommend that immunogenicity tests performed to support an approval application are conducted in patients with the greatest expected risk of developing adverse immune reactions, so that any extrapolated indications are for uses and patient populations where a lower risk would be expected, e.g. due to lower doses or shorter durations of use.[8, 14] As is the case with any medicine, including innovator biologics and biosimilars, regulatory authorities can request post-marketing surveillance studies to collect additional data on safety during routine clinical use, and some biosimilars have been approved in Europe with post-marketing surveillance requirements in place.

Assessing biosimilar safety in New Zealand

In New Zealand, manufacturers of all biological medicines (either original innovator medicines or biosimilars) are required to submit Periodic Benefit Risk Evaluation Reports, which compile new and emerging evidence about the risks and benefits of a medicine for approved indications.[18]

Quick-fire questions about biosimilar medicines

Are biosimilars just generic versions of a biological medicine?

No. Although they are alternative versions of a medicine developed after the patent has expired on the original product, they differ from generic medicines in that:

- Generic medicines have an identical chemical structure to a patented pharmaceutical; biosimilars are highly similar to an existing biological medicine, but not identical
- Since biological medicines are often large, complex structures it can be difficult to measure the physical and chemical similarity of a biosimilar version of a medicine compared to the innovator product due to analytical limitations

As a result, the approval process for biosimilars is more rigorous than the approval process for generic versions of a chemically synthesised medicine, and requires clinical tests of efficacy and safety.

Will patients have the same degree of clinical benefit if they take a biosimilar instead of the original biological medicine?

The approval process for biosimilars requires that the manufacturer demonstrate comparable clinical quality, efficacy and safety to a pre-existing, approved, reference medicine (usually, the original branded version of the biological medicine). When biosimilars are used for treating patients with conditions which have been directly studied in clinical trials there will be clinical evidence of comparable efficacy. When biosimilars are used for "extrapolated indications", which have not been directly assessed in clinical trials, the level of evidence that they will produce the same degree of clinical benefit is lower. However, in these cases there is an expectation that they will produce the same degree of clinical benefit on the basis of factors such as the chemical and physical similarity of the medicines, evidence from clinical studies showing similar pharmacodynamics and pharmacokinetics, and consideration of the mechanism of action of the original biologic in that indication.

Will the original biologics that the biosimilars are designed to replicate still be subsidised by PHARMAC?

This will vary on a case by case basis and will depend on the outcome of the competitive pricing process run by PHARMAC. Currently, two biosimilar medicines are funded in New Zealand, Zarzio (filgrastim) and Omnitrope (somatropin); the innovator versions of these medicines are no longer funded.

What do I do if a patient has adverse effects with a biosimilar or feels that it is not as effective?

If a patient has an adverse drug reaction to any pharmaceutical, a report should be submitted to the Centre for Adverse Reactions Monitoring (CARM). This is particularly important for newer medicines and can be done using the adverse reaction reporting tool via your practice management system, electronic forms via the New Zealand Pharmacovigilance Centre website (**https://nzphvc.otago.ac.nz/**), email (**carmnz@otago.ac.nz**) or using the pre-printed CARM adverse drug reaction report card.

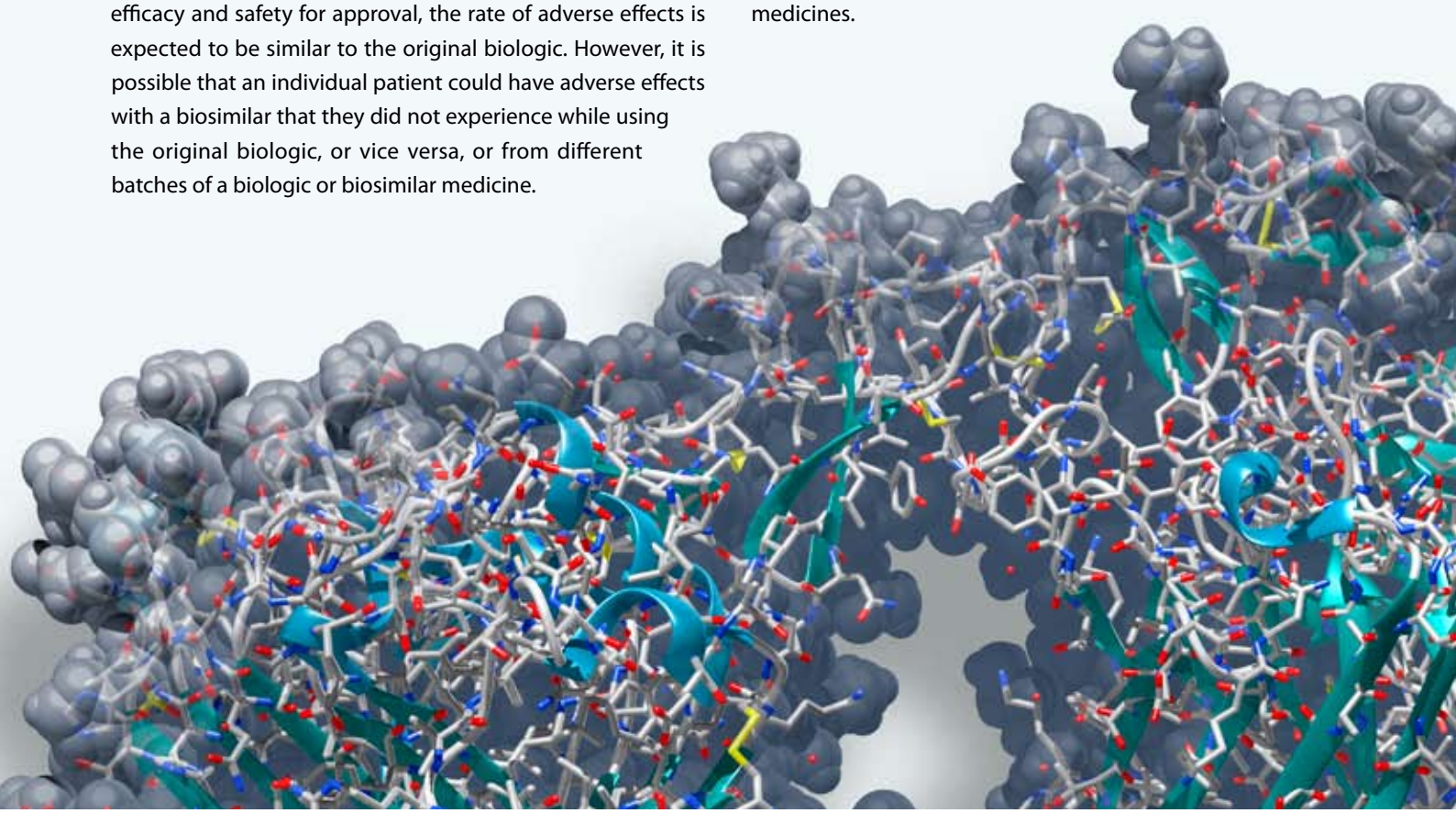
For further information on reporting adverse effects, see: "Adverse drug reactions" in the New Zealand Formulary: **www.nzf.org.nz/nzf_107**

As biosimilars are required to demonstrate comparable quality, efficacy and safety for approval, the rate of adverse effects is expected to be similar to the original biologic. However, it is possible that an individual patient could have adverse effects with a biosimilar that they did not experience while using the original biologic, or vice versa, or from different batches of a biologic or biosimilar medicine.

How do I switch a patient from a biologic to a biosimilar?

Most biologics currently in use require prescription and/or application for Special Authority approval to be completed by a specialist in an appropriate field, e.g. rheumatology, oncology. Hence decisions regarding switching a patient from using a biologic to a biosimilar will likely be managed in secondary care. General practitioners may be involved in follow-up and monitoring for adverse effects. Patients should be made aware that they are taking a different brand of biological medicine, and the patient, general practitioner and clinician who initiated the biosimilar should all be alert to the development of adverse effects or changes in clinical efficacy.

In many cases funding arrangements and cost to a patient are likely to dictate whether the original biologic or biosimilar are initially prescribed, similar to the case with brand name or generic medicines. The most likely cases where patients may switch from using a biologic to a biosimilar would be due to a funding change or if a clinician and patient decide to trial a biosimilar after a poor response or intolerance to the original biologic or vice versa; in these cases the alternative medicine may not be routinely subsidised and a Named Patient Pharmaceutical Assessment application for funding may be necessary. PHARMAC regularly seeks clinical input and consultation before changing funding arrangements for medicines.



Biosimilars currently subsidised in New Zealand

At present two biosimilar medicines are subsidised for use in New Zealand: a filgrastim biosimilar (Zarzio; recombinant human G-CSF) and a biosimilar version of somatropin (Omnitrope; recombinant human growth hormone). As with the original biologic medicines, both of these biosimilars require Special Authority approval with applications from a relevant specialist.

Zarzio is indicated for the treatment of neutropenia of various causes.[19] Zarzio has been compared with the original biologic Neupogen in studies in healthy males and females, and in females with neutropenia undergoing chemotherapy for the treatment of breast cancer.[20] At the time that PHARMAC announced it intended to subsidise Zarzio, it was estimated that it had been used by approximately 80,000 patients overseas without any safety concerns raised compared to the original biologic.[21] Zarzio is also approved for use in other regions, including Europe and the United States.

After approval and funding of Zarzio in New Zealand, PHARMAC estimated cost savings to be approximately $5 million per annum, despite an increase in usage of filgrastim of approximately 25%.[3] It is likely that similar trends will be seen with other biosimilars, and that the introduction of biosimilar versions of patented biologics may enable wider access to these medicines and improved health outcomes at a reduced overall cost.

Omnitrope is used for the treatment of short stature due to a variety of conditions: growth hormone deficiency, Prader-Willi syndrome, Turner syndrome, chronic kidney disease in children and adolescents and short stature without growth hormone deficiency.[19] It has been assessed in clinical trials in children with growth hormone deficiency, and its use in other indications is by extrapolation; the indications subsidised with Special Authority approval in New Zealand are similar to the approved uses of Omnitrope in Europe.[22] Omnitrope is also in use in other countries and has been approved for use in Europe and the United States.

Many other biologics will lose their patent protection soon

Given their relatively recent introduction to clinical practice, many biologics in use in New Zealand are still under patent. The biosimilars that have been approved for use in New Zealand are available due to patent protection expiring on the original biological medicine here. In other cases, the expiry of patent protection on biologics has led to price negotiations with manufacturers via a competitive tender process, with the result that the innovator biologic has continued to be funded at a lower cost , such as the sole supply funding decision for Remicade (infliximab).[23] A number of biologics will lose their patent protection within the next five years or so, which may lead to lower pricing through biosimilar competition, including:[24]

- Adalimumab (Humira)
- Bevacizumab (Avastin)
- Etanercept (Enbrel)
- Insulin detemir (Levemir)
- Insulin glargine (Lantus)
- Insulin glulisine (Apidra)
- Natalizumab (Tysabri)
- Pegfilgrastim (Neulastim)
- Rituximab (Mabthera)
- Teriparatide (Forteo)
- Trastuzumab (Herceptin)

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