Working title:

Biosimilars are coming: ready or not

John Zalcborg

Cancer Research Program, School of Public Health and Preventative Medicine,
Monash University, Melbourne, Victoria, Australia

Corresponding author: Professor John Zalcborg

Address: Public Health and Preventive Medicine

Monash University

553 St Kilda Rd

Melbourne VIC 3004

Phone: +61 3 99030388

Short title: Biosimilars in Australia

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List of acronyms

ADA	Anti-drug Antibody
ARA	Australian Rheumatology Association
CD	Crohn's Disease
ECCO	European Crohn's and Colitis Organisation
EMA	European Medicines Agency
FDA	Food and Drug Administration
IBD	Inflammatory Bowel Disease
mAb	Monoclonal Antibody
MOA	Mechanism of Action
PBS	Pharmaceutical Benefits Scheme
PD	Pharmacodynamics
PK	Pharmacokinetics
PRCA	Pure Red Cell Aplasia
RA	Rheumatoid Arthritis
TGA	Therapeutic Goods Administration
UC	Ulcerative Colitis

Introduction

Biologic medicines (biologics), produced using living organisms, represent a class of medicines used to treat a number of serious diseases, including diabetes, multiple sclerosis, rheumatoid arthritis (RA), and cancer. Some of the key biologics currently used in oncology are monoclonal antibodies (mAbs), which include trastuzumab, rituximab, and bevacizumab. Rituximab was the first mAb approved for the treatment of cancer and has had a substantial positive impact on the clinical outcome of patients with non-Hodgkin's lymphoma.¹ Biologics have also been routinely used in the supportive care of patients with cancer; these biologics include epoetin alfa and filgrastim.

Compared with small molecule drugs, the inherent complexities of developing and manufacturing biologics (usually large, complex biomolecules) has meant that treatment with biologics is costly and places a high burden on healthcare systems. In 2013, it was predicted that biologics would constitute 19–20% of the global therapeutics market by 2017.² Of the \$39.1 billion spent on oncology medicines in the US in 2015, 35% was spent on mAbs.³ Despite the efficacy of biologics for the treatment of cancer, their high cost and issues with availability and accessibility have limited patient access to some of these medications. In Australia, the high cost of biologics has limited their uptake to those indications reimbursed through the Pharmaceutical Benefits Scheme (PBS).

The European Medicines Agency (EMA) defines a biosimilar as a biological molecule containing “*a version of the active substance*” of an existing approved biologic, termed the ‘reference’ or ‘originator’ product.⁴ According to the Therapeutic Goods Administration (TGA), “*a biosimilar medicine is a version of an already registered biological medicine*” that has similar physicochemical, biological,

immunological, efficacy, and safety characteristics to the reference biologic. The US Food and Drug Administration (FDA) states that a biosimilar should be “*highly similar to the reference product*”, apart from “*minor differences in clinically inactive components*”, and that a biosimilar should have no “*clinically meaningful differences*” in terms of its safety, purity, and potency when compared with the reference product. Biosimilars are not identical copies of the reference biologic, although they are required to have the same amino acid sequence, and show similarity in post translational modifications and in higher order structure; yet biosimilars are not generics. In contrast to reference biologics, regulatory assessment of biosimilars is based on ‘similarity’ – a definition that focuses heavily on demonstrating structural and functional similarity to the reference biologic. Clinical pharmacokinetics (PK) and efficacy and safety studies then serve to confirm that there are no clinically meaningful differences between the biosimilar and reference biologic. The cost of developing biosimilars is usually lower than that of the reference biologic, due in part to the less extensive clinical development programme required to support regulatory approval.

In addition to legal protection provided by patents, reference biologics are also protected by defined periods of market exclusivity that are granted to drug manufacturers by regulatory authorities in order to encourage innovation; the duration of this protection varies by country.⁵ During this period, biosimilar manufacturers are prevented from marketing biosimilar versions of the reference biologic. With the patents and exclusivity periods for a number of key oncology biologics having expired or nearing end of term, the introduction of biosimilars has the potential to (1) increase patient access to these therapeutics, (2) substantially reduce costs in healthcare systems, and (3) extend the use of a biosimilar beyond its currently

marketed indication. It has been estimated that the use of biosimilars may result in cost savings between 50 and 100 billion EUR in Europe and the US.⁶ In Australia, the first biosimilars to gain regulatory approval were epoetin lambda and filgrastim, which were approved in 2010 (Fig. 1). Price modelling of selected biologics by Gleeson and co-workers estimated that drug expenditure could be reduced by as much as 24% through the timely introduction of biosimilars into the Australian market.⁷ The Australian government has indicated that the use of biosimilars could result in cost savings of up to \$880 million AUD between 2015 and 2020.⁸

Despite their obvious benefits, the uptake of biosimilars has been slow, even in Europe, which approved the first biosimilars in 2006. This slow uptake has been largely attributed to poor knowledge of biosimilars and a lack of acceptance of the concept of biosimilarity amongst clinicians.⁹ In Australia, there also appears to be some confusion regarding biosimilars and their approval process,¹⁰ suggesting that awareness of biosimilars could be significantly improved. The purpose of this review is to increase awareness about biosimilars amongst Australian clinicians, particularly in the field of oncology.

Differentiating biosimilars from generics

Unlike small-molecule drugs that are chemically synthesised, biologics are large and complex biomolecules produced in living organisms and then purified and characterised using state-of-the-art techniques. While the manufacturers of biosimilars may have access to the amino acid sequence of the reference biologic, the manufacturing process remains proprietary and has to be recreated using reverse engineering. The cell line, growth conditions, purification reagents, and methodology, as well as the storage conditions, can all have an effect on the activity and efficacy of

the final product. The inherent variability of expressing proteins in a living organism (owing to glycosylation and other post-translational modifications) and the subsequent complex manufacturing process are the main reasons why biosimilars are not 'identical' to their reference product. This should be contrasted with generics, which are chemically synthesised to be exact replicas of their patented originals. Hence, for the regulatory approval of generics, it is sufficient to demonstrate that they are structurally identical to the reference product. Biosimilars are required to demonstrate structural and functional similarity to the reference product to the extent that there are not expected to be any clinically meaningful differences in clinical safety and efficacy.

Establishing biosimilarity in Australia

In order to be approved, a biosimilar must undergo a series of rigorous assessments to establish similarity with the reference biologic. In Australia (as with Europe and the US),^{4, 11} biosimilars do not undergo the same approval process as the reference biologic. Instead, approval of biosimilars is based on the 'totality-of-the-evidence' concept (Fig. 2), which involves evaluating the similarity of physicochemical, preclinical, and clinical data from the biosimilar to that of the reference biologic.¹² Given the extensive knowledge base already compiled for the reference biologic, the aim of these studies is to confirm biosimilarity with the reference biologic, rather than to demonstrate the safety and efficacy of the biosimilar itself. Establishing biosimilarity with the reference biologic means that the biosimilar can often rely on the safety and efficacy profile of the reference biologic, resulting in abbreviated testing and approval processes.¹³

The TGA has developed a set of strict guidelines (which have been adopted from the EMA guidelines) to govern the assessment and approval of biosimilars.¹⁴ Analytical assays are used to establish the physicochemical similarity between the biosimilar and the reference product, through the comparison of primary and higher-order structure, size, charge, and post-translational modifications, while cell-based assays are used to compare function and biological activity.^{15, 16} The level of similarity established through physicochemical and biological characterisation then determines the nature and extent of the preclinical and clinical studies required; albeit such studies are usually much less demanding than those required for a novel biologic. Thus, compelling confirmation of biosimilarity from non-clinical data may reduce the magnitude of costly clinical investigations required.¹⁷

Initially, clinical studies are usually carried out to compare the PK and pharmacodynamics (PD) of the biosimilar with that of the reference biologic. The Australian/EMA guidelines recommend that the PD markers be chosen based on their relevance to the clinical outcome.⁴ The study population and study design are also carefully planned based on what is known about the PK/PD properties of the reference biologic, the disease's natural history and the results of the prior analytical studies. Finally, clinical studies assessing the efficacy and safety (especially immunogenicity) of the biosimilar relative to the reference biologic are conducted, all of which also serve to address any unresolved clinical uncertainties revealed by the analytical or PK/PD studies. Approval of a biosimilar is therefore granted based on the totality of evidence, which is the cumulative data compiled from analytical, preclinical, and clinical assessments of similarity (Fig. 2). In cases where there are several biosimilar versions of the same molecule, there is no regulatory requirement for biosimilars to be compared against one another.

Extrapolation of indications

In many cases, once biosimilarity has been established for one indication, a biosimilar may receive regulatory approval for another indication held by the reference product, without the need for a comparative clinical trial in that indication – this is known as extrapolation. The process of extrapolation removes the need for unnecessary clinical trials in other indications, thereby reducing the costs, resources, and time required for biosimilar development.¹⁸ This may translate into increased patient access to medication, through cost savings for both patients and healthcare systems, and a reduction in the time required for biosimilar approval. The American Society of Clinical Oncology recently issued a statement addressing several aspects of biosimilars, which also argues that extrapolation is necessary in order for cost savings to be generated. Despite the benefits of extrapolation, this practice has been met with skepticism from some clinicians. A number of other medical societies have expressed concerns about the safety and efficacy of a biosimilar in indications for which clinical data are available for the reference but not the biosimilar product.^{19, 20} Extrapolation from one disease to another can be particularly contentious. In 2013, the European Crohn's and Colitis Organisation (ECCO) argued that the clinical efficacy of a drug in inflammatory bowel disease (IBD) cannot be predicted based on its effectiveness in RA.²⁰ However, echoing the growing confidence in the EMA's approval process, the updated ECCO position statement in 2017 states that “*clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation*”.²¹ It is worth noting that extrapolation is not a new concept but an established regulatory principle that has been used to reconfirm the safety and efficacy of reference biologics following changes in their manufacturing process.¹³ There are

strict regulations governing extrapolation – approval for each indication is evaluated on a case-by-case basis and requires rigorous scientific justification. Approval of a biosimilar for one indication does not automatically result in approval for all other indications of the reference biologic. The TGA framework is based on the EU guidelines: “*Justification will depend on e.g., clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications. Possible safety issues in different subpopulations should also be addressed.*” The mechanism of action (MOA) of a drug is of particular importance when deciding whether extrapolation should be granted. Extrapolation is often easier to achieve for a biosimilar with a well-understood MOA.¹³ Filgrastim (Neupogen[®], Amgen, Thousand Oaks, CA, USA) is used for the treatment of neutropenia and to mobilise peripheral blood progenitor cells in patients. Given that the pharmacologic actions of filgrastim are understood to be mediated through a single receptor, similar levels of receptor binding by the biosimilar and the reference biologic may be expected to result in a similar clinical effect. Combined with the high degree of similarity between the biosimilar filgrastim and the reference biologic in terms in molecular structure, PK, PD, safety, and immunogenicity, this formed the basis for approval in the prevention of chemotherapy-induced neutropenia and through extrapolation to the mobilisation of peripheral blood progenitor cells being granted by the EMA.²²

Compared with simpler biologics such as filgrastim, achieving extrapolation can be more challenging for molecules such as mAbs, which have a more complex structure, and MOAs that may involve different parts of the molecule.¹³ Therapeutics with a poorly understood or complex MOA may necessitate additional functional and/or clinical data to achieve extrapolation. The first mAb biosimilar to be approved by the

EMA was CT-P13, an infliximab biosimilar for the treatment of autoimmune and inflammatory diseases.²³ Extrapolation of the similarity in efficacy of CT-P13, established in RA, to the IBD setting was controversial because of an observed difference in the binding affinity of CT-P13 (compared with infliximab) for the Fc γ RIIIa receptor. This receptor may be involved in antibody-dependent cell-mediated cytotoxicity, and potentially impact IBD. As a result of this finding, Health Canada initially failed to grant extrapolation of CT-P13 to Crohn's disease (CD) and ulcerative colitis (UC). In contrast, the EMA granted extrapolation of CT-P13 to all eligible indications of infliximab.²² This decision was based on the fact that the difference in Fc γ RIIIa binding was not present under physiological conditions. In 2016, Health Canada extended approval of CT-P13 to CD and UC.

Immunogenicity

One of the key safety considerations for granting approval and in considering extrapolation of a biosimilar is its immunogenicity. Significant differences in the immunogenicity of a biosimilar and the reference biologic may translate into differences in both efficacy and safety.²⁴ The importance of immunogenicity is exemplified by the significant increase in the number of cases of pure red-cell aplasia (PRCA) observed following treatment with epoetin (Eprex[®], Janssen-Cilag, High Wycombe, United Kingdom) between 1998 and 2003.²⁵ The increase in cases of PRCA was a result of a change in the formulation of Eprex[®]; albumin had been replaced by polysorbate 80 and glycine, following regulatory concerns that use of human serum albumin might transmit variant Creutzfeldt–Jakob disease. This formulation change resulted in the generation of neutralising antibodies that cross-reacted with endogenous erythropoietin, leading to PRCA.²⁵

The immunogenicity of a biosimilar can be compared to that of the reference biologic using both *in vitro* and *in vivo* methods, as was demonstrated recently for CT-P13.²⁶ CT-P13 and its reference (infliximab) were shown to have similar recognition profiles when tested against an array of antibodies raised against infliximab peptides. Furthermore, anti-drug antibodies (ADAs) isolated from infliximab-treated patients were shown to cross-react with CT-P13.²⁶ Quantification of ADAs elicited in patients receiving CT-P13 or infliximab in head-to-head trials revealed similar proportions of patients with ADAs and similar rates of ADA formation and AEs in each treatment group.²⁶ It has been suggested that differences in the immunogenicity of a molecule are primarily a function of its physicochemical characteristics,¹⁷ further underscoring the importance of analytical assessments undertaken early in the process of establishing biosimilarity (Fig. 2).

Impact of biosimilars in Australia

As observed in other countries, the major benefit of switching to oncology biosimilars in Australia will be the increased access to treatments in part related to a reduction in costs to the patient and to the healthcare system. Compared with generic versions of small-molecule drugs, the cost savings from the uptake of biosimilars is likely to be smaller in magnitude, given the higher costs of developing and manufacturing these complex pharmaceuticals. However, in view of the high cost of biologics, the savings from using biosimilars are still likely to be substantial. Apart from cost savings by virtue of their lower development costs, biosimilars can also affect the pricing of the reference biologic through competition. For example, the price of filgrastim in Australia fell by 62% (over 6 years) following the entry of three competing biosimilars into the market.⁷ Approximately half (52%) of the total PBS expenditure

on filgrastims in 2015–2016 was for the biosimilar versions, indicating substantial uptake of these biosimilars.⁷

Biosimilars such as filgrastim, which were used in supportive care, were among the first to be approved in Australia, Europe, and the US; the first biosimilar versions of mAbs for oncology have only recently been granted regulatory approval in these regions. In November 2017, the first rituximab biosimilar, Riximyo[®] (Sandoz GmbH, Kundl, Austria) was approved by the TGA for the treatment of B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.²⁷ Of note, the PBS expenditure (as publicly disclosed) for rituximab during the 2015–2016 financial year was ~\$270 million AUD.⁷ Given the recent entry of the rituximab biosimilar into the Australian market, the impact of its approval on pricing can only be estimated at this stage. Modelling by Gleeson and co-workers suggested that if a rituximab biosimilar had been available in 2015–2016, it would have resulted in a saving of ~\$43 million AUD.⁷

To assess the real-world impact of biosimilars that modify disease processes, it is helpful to examine biosimilars used in the treatment of autoimmune and inflammatory diseases, which have been available in Australia for several years. Following TGA approval of the first infliximab biosimilar in August 2015, the price of the reference biologic decreased by 27%.⁷ Biosimilars of rituximab and other mAbs may well deliver similar cost reductions to oncology treatment. In fact, several other oncology biosimilars (Table 1) are currently in late-stage clinical development, including two biosimilars of trastuzumab, CT-P6 and Myl1401O, for the treatment of HER2-positive breast cancer. In recent phase 3 equivalence studies, both CT-P6²⁸ and Myl1401O²⁹ were shown to have similar efficacy to trastuzumab (reference) in patients with HER2-positive breast cancer.

Awareness and acceptance of biosimilars in Australia

Although the first biosimilar was approved for use in Australia in 2010 (Fig. 1), a recent survey conducted by the Alliance for Safe Biologic Medicines revealed a lack of awareness amongst clinicians and concerns surrounding biosimilar use.¹⁰ In a survey of 160 prescribers in Australia, only 21% of respondents indicated that they were very familiar with biosimilar medicines while 73% of respondents indicated that they had only a basic understanding of biosimilar medicines.¹⁰ Furthermore, approximately half of the respondents incorrectly believed that biosimilar medicines underwent the same regulatory approval process as the reference biologic.¹⁰ A total of 73% of respondents indicated that they would have some concerns with prescribing biosimilars in indications for which regulatory approval was granted through extrapolation.

In an effort to increase clinician and patient confidence in the use of biosimilars, in May 2015, the Australian government dedicated \$20 million AUD towards activities to raise awareness of biosimilars.³⁰ As part of its efforts to encourage the use of biosimilars, Australia's Pharmaceutical Benefits Advisory Committee recently indicated that some biosimilars may be substituted for the reference biologic at the pharmacy level, provided certain conditions were met – a practice known as 'a' flagging. This is similar to the concept of 'interchangeability' in the US, as defined by the FDA; however, the requirements for a biosimilar to be deemed 'interchangeable' are more stringent than those for the establishment of biosimilarity.³¹ Currently, the FDA has not approved any biosimilar as being interchangeable with its reference biologic.³² In Australia, a number of clinician groups, including the Australian Medical Association and the Australian Rheumatology Association (ARA), have

expressed concerns about the recommendation for 'a' flagging.³³ Specifically, the ARA has indicated that although switching from a reference biologic to its biosimilar is supported by evidence, there is currently no evidence to support the safety and efficacy of repeated switching, which expert clinicians and regulators alike suggest is to be avoided.³⁴ Although a few studies have examined switching of reference anti-rheumatic mAbs with their biosimilars,³⁵ it is clear that more research is required to fully understand the potential risks and benefits of multiple switches.

Potential innovation-driven opportunities with biosimilars

Many of the pharmaceutical companies that manufacture and develop biosimilars are, in fact, established manufacturers of reference biologics applying their expertise to biosimilar development. As additional biosimilar versions of the same reference biologic become available, companies may seek to identify advantages of their product over competitor biosimilars. The additional competition arising from the introduction of biosimilars will also provide opportunities for industry (particularly manufacturers with a strong history of innovation) to generate new efficacy and safety data for biosimilars in indications that were not previously explored with the reference biologic. These opportunities are likely to be driven by the increased knowledge base that has been accumulated since the reference biologic was first introduced. For example, Celltrion are exploring the potential for their infliximab biosimilar, CT-P13, to be administered subcutaneously, a formulation that is not currently available for the originator product. The presence of a large number of cancer cooperative trial groups³⁶ mean that Australia is ideally suited for conducting such exploratory trials in a very cost-effective manner, thereby providing potential benefits to the community

and patients. Funded in part by the Australian government (Cancer Australia), these investigator-led trial groups seek to enhance the knowledge base in oncology.

Conclusions

The relationship between a biosimilar and reference biologic is different to that between a generic and the originator version of a small-molecule drug, necessitating a distinct approach to the regulatory assessment and approval of biosimilars. There is a strict regulatory framework in place governing the approvals of biosimilars for use in Australia. The availability of biosimilars has the potential to bring substantial savings to the Australian healthcare system, providing an opportunity for increased patient access to treatment and broader use of biosimilars compared with reference biologics. Further education of clinicians and patients may be required to increase understanding and instil greater confidence in the use of biosimilars.

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Figure legends

Fig. 1. Biosimilars approved by the Therapeutic Goods Administration (TGA) of Australia to date (April 2018)

Biosimilar medicines subsidised under the Pharmaceutical Benefits Scheme are indicated in bold.

Fig. 2. The totality-of-evidence approach for demonstrating biosimilarity

Table 1. Biosimilar cancer therapies currently in late-stage clinical development

Reference	Biosimilar	Clinical trial identifier (Phase 3 trials)	Indication
Rituximab	CT-P10 (Celltrion)	NCT02162771	Follicular lymphoma
		NCT02260804	
	GP2013 (Sandoz)	NCT01419665	Follicular lymphoma
	PF-05280586 (Pfizer)	NCT02213263	Follicular lymphoma
	ABP 798 (Amgen)	NCT02747043	Non-Hodgkin's lymphoma
Trastuzumab	CT-P6 (Celltrion)	NCT02162667	HER2-positive breast cancer
	Myl1401O (Mylan)	NCT02472964	HER2-positive breast cancer

	SB3 (Samsung Bioepis)	NCT02149524	HER2-positive breast cancer
		NCT01989676	HER2-positive breast cancer
	PF-05280014 (Pfizer)	NCT02187744	
	ABP 980 (Amgen and Allergan)	NCT01901146	HER2-positive breast cancer
Bevacizumab	ABP 215 (Amgen and Allergan)	NCT01966003	Non-small-cell lung cancer
	PF-06439535 (Pfizer)	NCT02364999	Non-small-cell lung cancer

HER2, human epidermal growth factor receptor 2

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Zalcborg biosimilars oncology au Figure 2.jpg

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Author/s:

Zalcberg, J

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