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REVIEW

A consensus statement on the use of biosimilar medicines in hematology in Australia

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Abstract

Despite their availability for over a decade, the exact nature of biosimilar medicines is still poorly understood with paucity of clear treatment guidelines for their use in clinical practice in Australia. Although hematologists have had experience with biosimilars in the setting of supportive care, with the approval of the first biosimilar rituximab in hematological malignancies, it is important to revisit this topic. To inform the use of biosimilar medicines in clinical practice, we have developed a consensus statement from an Expert Panel of Australian hematologists, oncologists, and cancer pharmacists. These recommendations address the approach to use of biosimilar products in place of the corresponding reference medicine in a number of different clinical contexts. Our recommendations are based on the premise that biosimilar medicines can be considered therapeutically equivalent to their reference brand and used in a similar way to the reference product in any approved indication. We advocate for local approaches to the provision of patient information, dispensing of the intended brand and pharmacovigilance, to be developed in consultation with local hematologists and aim to improve confidence in the appropriate use of biosimilar medicines and their expected outcomes among hematologists.

KEYWORDS

biosimilars, consensus statement, hematology

1 | INTRODUCTION

The first biosimilar medicines became available in Australia a decade ago.[1] However, despite awareness initiatives undertaken by the Australian government, recent research indicates that a thorough understanding of the science underpinning biosimilars remains lacking, and there is a need for protocols guiding their usage in clinical practice.[2,3]

Clinicians in Australia are familiar with biosimilars of epoetin lambda and filgrastim in the supportive care context. However, the first disease-modifying biosimilars in hematology are only now entering the

market, with the Therapeutic Goods Administration (TGA) approval of rituximab biosimilars for the treatment of B-cell non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia, as well as Pharmaceutical Benefits Scheme (PBS) reimbursement for all CD20 positive B-cell lymphoid cancers, including acute lymphoblastic leukemia.[4-6]

Concerns have been raised in the published literature regarding the use of biosimilars,[7] including a lack of confidence that biosimilars will provide equivalent therapeutic outcomes for patients,[2,7] use in indications that have been approved based on extrapolation of clinical data for the reference medicine, as well as perceptions of risk in "switching" of patients already receiving one brand of a biologic medicine to a biosimilar brand.[7]

This article aims to address these common concerns regarding biosimilar medicines, and provide a set of recommendations to guide the best-practice use of biosimilars in the treatment of hematological conditions in Australia.

2 | METHODS

A group of hematologists, oncologists, and pharmacists was convened from across Australia. The expert panel discussed, debated, and gathered consensus on topics that require clarification for clinicians and are considered controversial in the use of biosimilar medicines in hematological disorders in Australia.

The Australian Department of Health has performed and maintains a comprehensive systematic literature review on the topic of biosimilar medicines.[8] Therefore, it was agreed to utilize this as the basis for the Consensus Statement and no new literature search was performed. The expert panel participated in a teleconference meeting to discuss the potential scope of the publication and identify topics that would benefit from the development of consensus recommendations.

Subsequent to the first teleconference meeting, a modified Delphi methodology was employed to gain author consensus on the identified topics.[9,10] Multiple-choice voting options were mapped from each topic the panel discussed, to form the basis of the expert panel recommendations. Authors voted on the options for each recommendation, and any amendments suggested were collated for review in subsequent rounds of voting.

Accepting or omitting a recommendation required a predetermined minimum of 80% consensus from all authors. Authors could also suggest new recommendations, to be reviewed by the group in subsequent rounds. The statements that called for amendments or did not reach an 80% consensus were modified and subjected to a second round of voting. Those that gained 80% consensus were accepted as consensus recommendations.

After two rounds of online voting, a second teleconference meeting discussed disputed points or any outstanding topics. Successive rounds of discussion and live Delphi voting were conducted at the teleconference meeting until 80% consensus was reached to either accept or omit a voting point. The final consensus recommendations that gained more than 80% consensus from the authors are included in this manuscript.

3 | NARRATIVE REVIEW OF THE EVIDENCE

A narrative review of the literature on biosimilar medicines is provided below to support the consensus recommendations, based upon the systematic literature search commissioned by the Department of Health.[8]

3.1 | What are biologic and biosimilar medicines

3.1.1 | Biologic medicines

Biologic medicines are defined as pharmaceutical products that contain one or more active substances that are derived from living cells or organisms (eg, therapeutic proteins such as monoclonal antibodies).[11]

Compared to traditional synthetic pharmaceuticals, biologic medicines have large and highly complex molecular structures, which are sensitive to small environmental variations during their production.[12] Furthermore, the production within living systems results in variability in the final structure of individual molecules of the medicine, which is referred to as "microheterogeneity."[7,13,14] In addition, the make-up of the microheterogeneous molecules will vary slightly between each batch of the medicine manufactured, referred to as "batch-to-batch variation."[7,13,14]

These variations are well-understood and controlled by manufacturers, but nevertheless preclude each batch of a biologic medicine from being identical to another. This sets biologic medicines distinctly apart from small molecule drugs, which can be exactly replicated each time they are synthesised.[7,12-14]

Furthermore, changes to the manufacturing process of a biologic medicine have been shown to result in changes to the molecular structure over time (Figure 1).[15] Such changes are commonplace over the lifecycle of the majority of biologic medicines, and can vary from relatively low risk (eg, moving manufacturing equipment elsewhere in the facility) to high risk (eg, developing a new cell line for the product) (Figure 2).[16] Manufacturing process changes are regulated through a "comparability exercise" that compares the pre- and postchange product to ensure any differences do not lead to negative impacts for patients, and it is this regulatory experience that forms the basis for the concept of biosimilarity.[16]

As legal patents and market exclusivity periods for biologic medicines expire, it opens up possibilities for competitor manufacturers to introduce their own versions of these medicines to the market. The aim being to reduce costs to healthcare systems and potentially increase patient access to these expensive therapeutics. In the case of biologic medicines, these follow-on products are referred to as "biosimilar medicines" or "biosimilars."[7,11-13,17]

3.1.2 | Biosimilar medicines

A biosimilar medicine is a highly similar version of an already registered biological medicine (known as reference biological medicine)[11] and is described by the TGA to possess similar "physicochemical, biological, immunological, efficacy, and safety" characteristics as its reference biologic.[11,17]

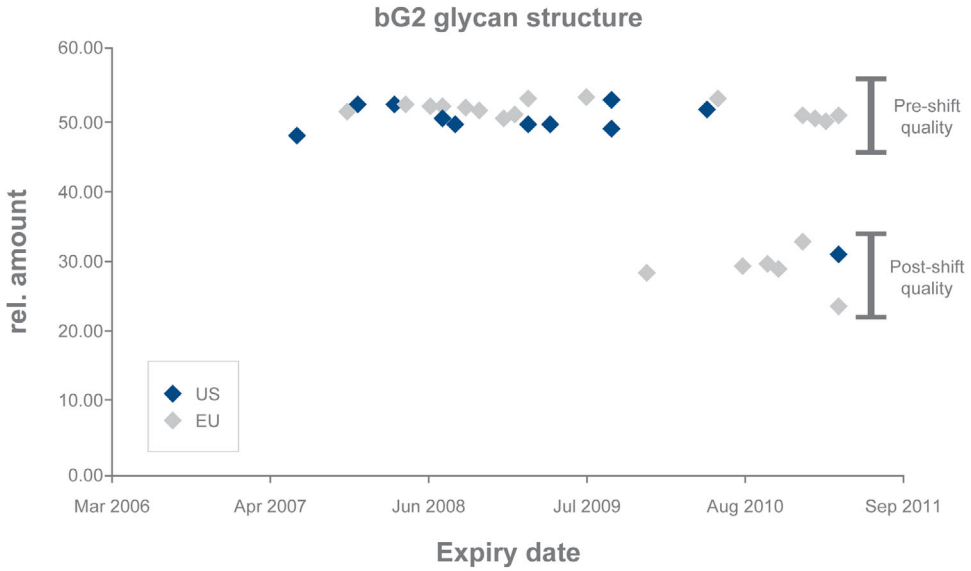

FIGURE 1 Analyzing complex product attributes over time. The bG2 glycan structure was quantified by Sandoz in many batches of commercial product distributed by the originator in the European Union (light blue) and the United States (dark blue). Expiry date of the product batches is listed on the *x*-axis and relative amount of product attribute enrichment is listed on the *y*-axis. Preshift quality refers to the content of the attribute prior to a manufacturing change and postshift quality after the manufacturing change. Adapted from McCamish and Woollett.[15] [Colour figure can be viewed at wileyonlinelibrary.com]

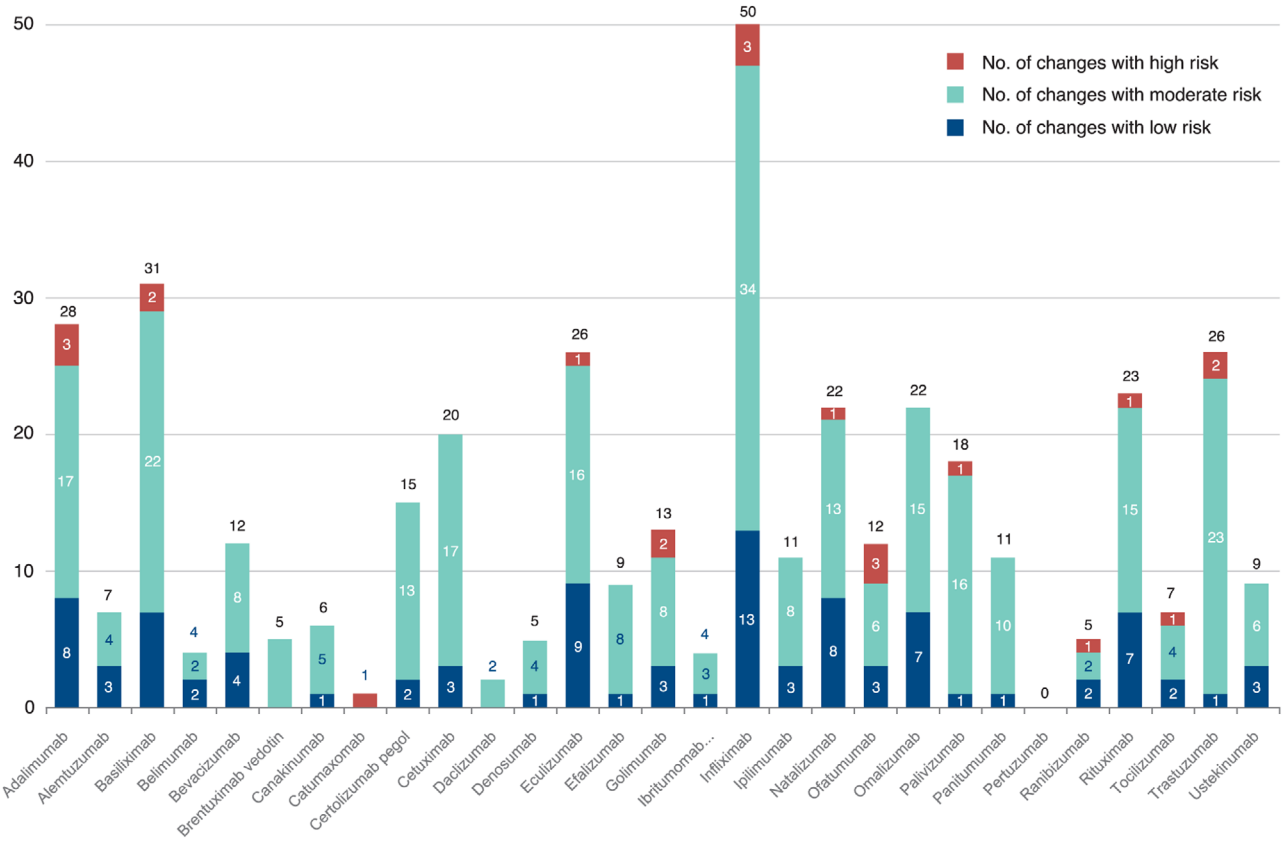

FIGURE 2 The number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category. All nonproprietary names relate only to the trade named medicines. Figure adapted from Vezer et al.[16] [Colour figure can be viewed at wileyonlinelibrary.com]

Biosimilars are designed to resemble the structural and therapeutic characteristics of a reference biologic.[12] However, unlike with generic versions of small-molecule medicines, the natural variation and manufacturing intricacies associated with biologic medicines impede biosimilars from being identical to the reference molecule.[7,12,13] Consequently, establishing biosimilarity requires more rigorous regulation processes than those applied to generic medicines to consider all critical quality attributes (ie, those impacting the function of the molecule) and demonstrate that no clinically meaningful differences exist and that the biosimilar molecule is therapeutically equivalent to the reference medicine.[7,11-17]

3.2 | Potential for cost savings

In 2015, 25% of the Australian PBS budget was spent on biologic medicines.[18] The cost of biologic medicines is often higher than that of small-molecule drugs due to complex development process encompassing research and development, working with mono- or multicellular cultures and complex downstream purification processes.[12]

In contrast, biosimilars already have an accessible reference molecule to match and can undergo a more streamlined clinical trial program, thereby cutting down development costs and enabling biosimilar manufacturers to offer reduced prices compared to their reference products.[18] The Australian Government has forecast biosimilars to save the PBS AUD $330.8 million from 2017 to 2022.[19]

Upon market entry of a biosimilar in Australia, both the reference product and biosimilar undergo a statutory price reduction of 25%.[20] At the hospital or pharmacy level, further discounts can be offered by manufacturers as a result of competition among brands. Further price reductions apply under PBS price disclosure arrangements if there is significant market competition on price; however, these rely on uptake of biosimilar medicines.[20,21]

Cost savings from the first generation of biosimilars are already being realized in Australia. For example, filgrastim has undergone a nearly 80% price reduction since the first biosimilar entry in 2010 (price of 20 syringes each containing 300 micrograms of filgrastim: AUD $3054 in 2010 to AUD $619.20 as of September 2019).[22,23] Cost savings such as these could be reinvested into the healthcare system to allow greater patient access to treatment.[20,21]

Internationally, in countries where biosimilar medicines have been available for longer, the impacts on the healthcare systems are more visible. The introduction of biosimilar filgrastim increased patient access by 44% in the European Union between 2006 and 2013,[24,25] and all European countries have seen an increase in use of filgrastim since biosimilar market entry.[26] In the United Kingdom, Sweden, and New Zealand, uptake of biosimilar filgrastim has led to a fivefold increase in patient access with concomitant budget savings.[26] Similarly, rituximab biosimilar uptake in the United Kingdom in 2017 alone delivered savings worth £50.43 million, one fifth of the total target of £250 million, enabling better saving of resources to create further treatment opportunities for patients.[27]

3.3 | Development and clinical confirmation of biosimilarity

Biosimilars are developed through physicochemical analysis of the reference product, with multiple iterations of process change and characterization comparison to develop a highly similar molecule.[28] It is a requirement of the TGA that any biosimilar has an identical amino acid sequence to the originator, and that all quality attributes associated with function and pharmacological activity fall within the established boundaries of variation for the reference product.[11,29,30]

A biosimilar manufacturer initially analyzes multiple batches of the reference product to understand its quality profile and the extent of its variability across different quality attributes over time. The limits of this distribution of reference product attributes then form the "goalposts" for development of the biosimilar (Figure 3).[31] If the attributes of the developed biosimilar fall within the acceptable range of variability of the reference molecule, then the biosimilar can be considered "highly similar."[7,11,28-31]

A stepwise approach is undertaken to demonstrate biosimilarity of a candidate biosimilar to the reference medicine. This begins with extensive physicochemical characterization and comparison of both products, followed by in vitro studies to test binding and activation (or inhibition) of physiological targets of the biosimilar molecule. The third step is to perform comparative clinical studies to confirm biosimilarity and to address any questions that may remain from previous analytical or functional studies.[7,11,28-30]

Biosimilar clinical trials must be head-to-head with the reference product in a population that is sensitive to detect any clinically meaningful difference by having fewer factors that cause major interindividual or time-dependent variation.[11,29,30] Because the intent is to show neither decreased nor increased activity, an equivalence design (ie, a two-sided test rather than non-inferiority) is usually preferred.[29,30] The primary endpoint is chosen for its sensitivity to display difference between the products, not necessarily its relevance to clinical practice[7,29,30] (eg, in hematology clinical trials, overall response rate [ORR] may be chosen in preference to progression-free survival [PFS] or overall survival [OS]). It is important to remember that the purpose of these clinical trials is to confirm biosimilarity to the reference molecule, not establish de novo clinical benefit, as this has already been established for the reference molecule.[7]

Recently, such trials to establish biosimilarity in hematology have been published for rituximab biosimilar GP2013 (Sandoz) and CT-P10 (Celltrion) where primary endpoints were equivalence in overall response rate.[32,33] In these trials, summarized in Table 1, the biosimilars achieved the primary endpoint, established therapeutic equivalence, and matched the safety profiles of the reference rituximab demonstrating their viability as successful alternatives.

3.4 | Timeline of biosimilars and approvals in Australia

Biosimilar regulation in Australia has largely followed that of Europe, where the European Medicine Agency (EMA) established regulatory

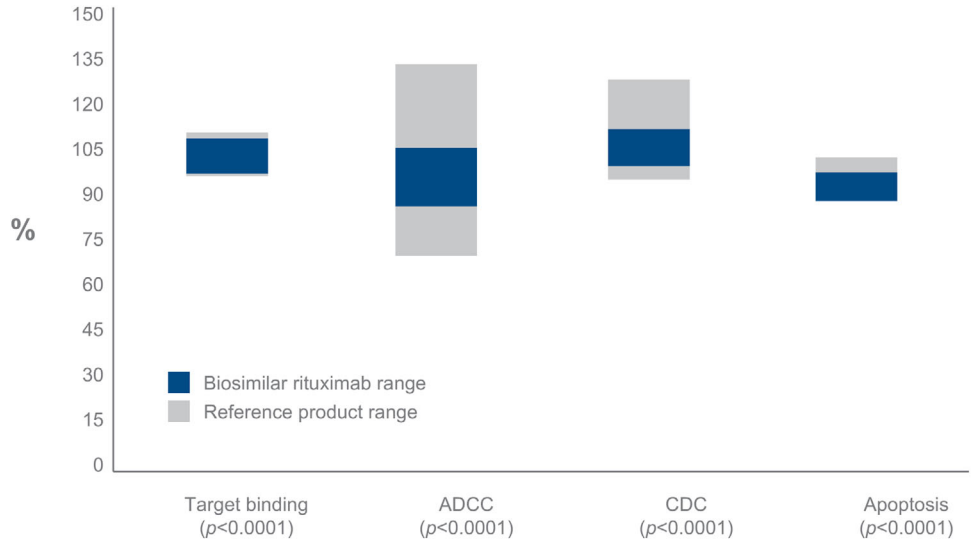

FIGURE 3 Potency bioassays designed to give quantitative results assessed using the two-sided test procedure (TOST) with bioequivalence limits of 0.8-1.25. The corresponding *P*-values were all highly significant (<.0001) confirming bioequivalence between biosimilar rituximab and the reference product. Figure adapted from Visser et al.[31] Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement dependent cytotoxicity
[Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Summary of trials comparing biosimilar rituximab to reference rituximab in follicular lymphoma (FL)[32,33]

Phase III trial	Participants	Regimen, N	ORR (primary endpoint) in ITT population	Safety	Antidrug antibody
NCT01419665 The ASSIST-FL trial:[32] Biosimilar rituximab GP2013 (Sandoz) vs reference rituximab	Previously untreated, advanced-stage, CD20+, stage III or IV FL	GP2013-CVP, 314	87%	Neutropenia: All grades—26% Grade III/IV—18%	2%
		Reference rituximab-CVP, 315	88%	Neutropenia: all grades—30% Grade III/IV—21%	1%
NCT02162771 Biosimilar rituximab CT-P10 (Celltrion) vs reference rituximab[33]	Previously untreated, advanced-stage, CD20+, stage III or IV FL	CT-P10-CVP, 70	96%	Neutropenia: All grades—45% Grade III/IV—28%	4%
		Reference rituximab-CVP, 70	90%	Neutropenia: all grades—28% Grade III/IV—17%	3%

Abbreviations: CVP, cyclophosphamide, vincristine, and prednisone.

guidelines for the approval of biosimilars separate from small-molecule generics in 2005.[1] In 2008, the Australian TGA adopted the EMA guidelines on the regulation of biosimilars, and to this day adopts many of the product class-specific EMA guidelines for assessment of biosimilar medicines. In 2013, the TGA published their own documentation on the evaluation of biosimilars, which was updated in 2015 (Figure 4).[1,34]

To date, there has been significant experience with biosimilar medicines in hematology in Australia in the supportive care setting with epoetins and filgrastims. Most recently, biosimilars of disease-modifying therapeutic antibodies have been approved or are under evaluation by the TGA, and these represent the next horizon for biosimilars in hematology.[1,34,35]

3.5 | Regulation and reimbursement of biosimilars in Australia

Under TGA regulations, the approval process of biosimilars is based on a "totality of evidence" approach, taking into account comparisons with the reference product in terms of the biosimilar's physicochemical structure, biologic function, preclinical and clinical pharmacokinetic, and pharmacodynamic (PK/PD) data, efficacy, safety, and immunogenicity evidence (Figure 5).[11,17,29]

In principle, the reference medicine's entire clinical development program does not need to be repeated for a given biosimilar. The safety and efficacy of the reference biologic has already been established in

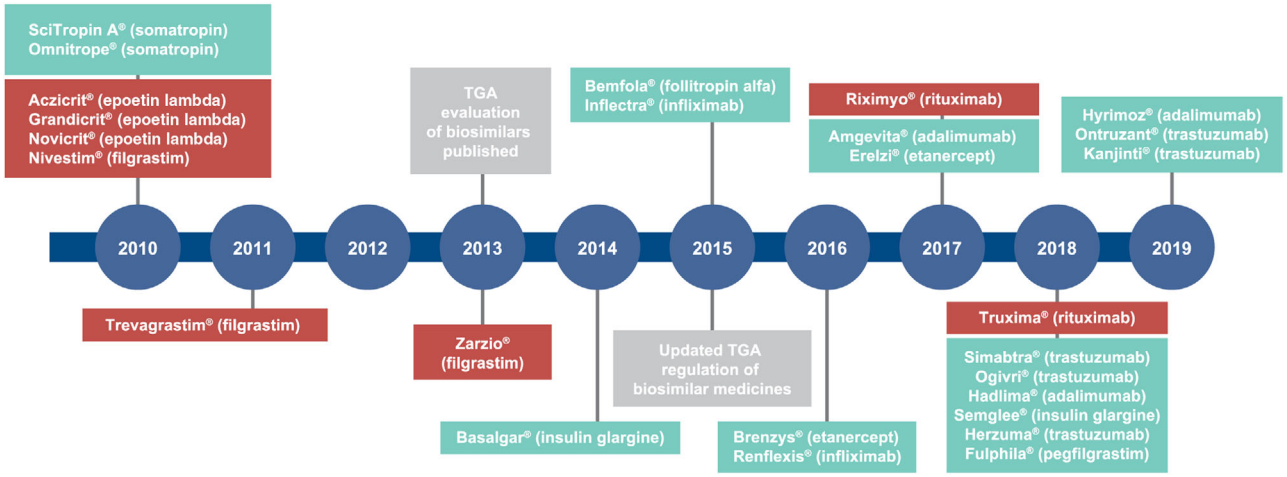

FIGURE 4 Biosimilars approved by the Therapeutic Goods Administration (TGA) of Australia to date (September 2019). Riximyo (Sandoz) is also registered under the brand names Rixonfya® and Rixvyda®. Truxima (Celltrion) is also registered under the brand names Ritemvia®, Rituzena®, and Tuxella®. Red = biosimilar medicines used in hematology. Teal = biosimilar medicines used in other disease areas. Grey = publication of TGA regulatory guidelines. Figure adapted from Australian Department of Health. Which biosimilar medicines are available in Australia?[34] [Colour figure can be viewed at wileyonlinelibrary.com]

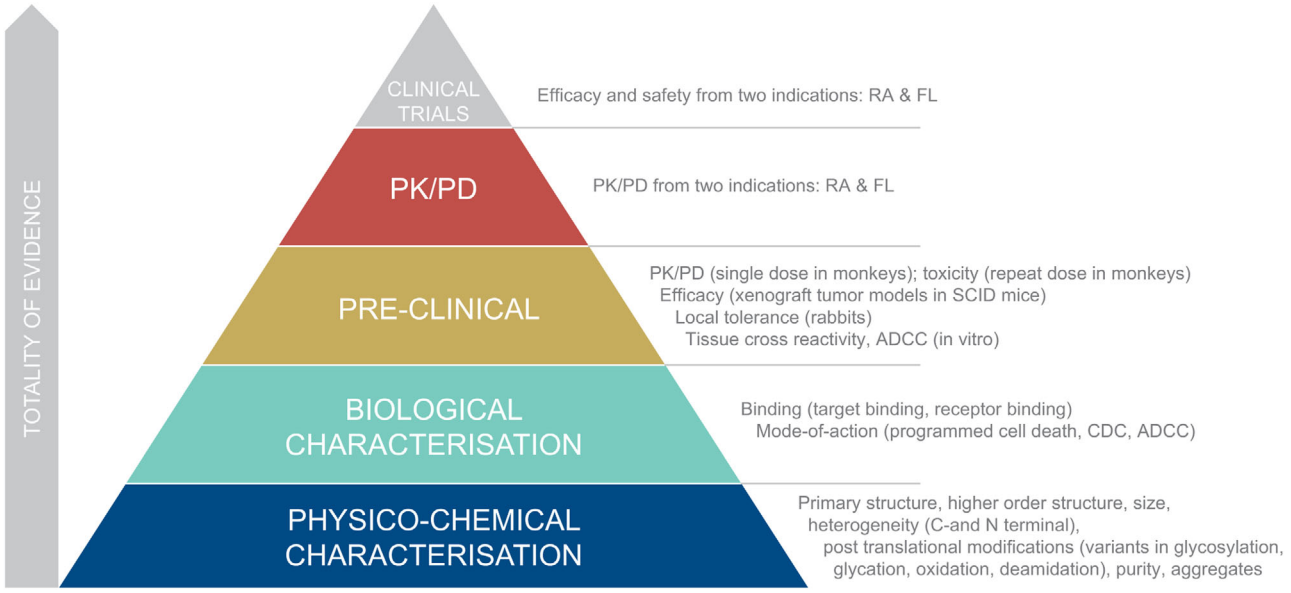

FIGURE 5 The totality of evidence approach adapted by the TGA requiring multiple levels of characterization of a biosimilar before approval. This figure shows Sandoz biosimilar rituximab as an example. Figure created from multiple sources.[5,11,17,29] Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement dependent cytotoxicity; FL, follicular lymphoma; RA, rheumatoid arthritis; SCID, severe combined immunodeficiency
[Colour figure can be viewed at wileyonlinelibrary.com]

all its indications. A phase III trial in a single indication serves the purpose of confirming the biosimilarity established in previous steps and eliminating any residual possibility of difference in clinical safety or immunogenic response.[7,17,29]

Therefore, once biosimilarity is established on the basis of the totality of evidence, it may be possible for a biosimilar to be approved in other indications of the reference product.[17,29] This process is sometimes referred to as "indication extrapolation," but more accurately describes extrapolation to the biosimilar of the reference product's clinical data in other indications.[7,17,29] The TGA considers each biosimilar medicine application for extrapolation on a case-by-case basis.[17]

Such extrapolation is not unique to biosimilars but rather is an established regulatory and scientific principle. For example, when new subcutaneous formulation of a hitherto intravenously (IV) administered medicine (such as reference rituximab) is submitted, a single clinical study is usually sufficient to grant approval in all indications of the IV product.[7]

TABLE 2 Table of recommendations

Recommendation	Rationale
Recommendation 1	
Clinicians can consider a biosimilar medicine that has been approved by the TGA to be therapeutically equivalent to its reference product, with demonstrated comparability in terms of quality, PK/PD, efficacy, safety, and immunogenicity. Equivalent clinical outcomes can be expected for an individual patient whether the reference product or a biosimilar is used.	Biosimilar medicines in Australia are regulated by the TGA, who assess each biosimilar on the basis of the totality of data, comparing it to the reference product, including physicochemical analysis, preclinical, and clinical trials.[17,29]
Recommendation 2A	
Extrapolation of clinical data from the reference product to the biosimilar medicine across indications is based upon established scientific principles. Clinicians can expect equivalent therapeutic outcomes from an approved biosimilar as they can from the reference biologic, regardless of whether it is being used in an extrapolated indication or an indication studied as part of the biosimilar's clinical trial program.	The regulatory principle of extrapolation is successfully used outside of the realm of biosimilars. For example, the subcutaneous formulation of reference rituximab was approved by the TGA for use in both follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), on the basis of one Phase I and one Phase III trial, both in FL.[42] In the case of biosimilars, postapproval real-world evidence has confirmed that use in extrapolated indications is safe and effective, for example, with the use of biosimilar filgrastim in extrapolated indications such as stem cell mobilisation[43] and biosimilar infliximab in inflammatory bowel disease.[44]
Recommendation 2B	
If the TGA has approved a biosimilar brand of rituximab for the treatment of DLBCL, whether via extrapolation or through a direct clinical study in that indication, it is because the biosimilar has demonstrated therapeutic equivalence to the reference product across the totality of evidence. Clinicians can therefore expect equivalent clinical outcomes for that biosimilar rituximab as they would for the reference product, in DLBCL as in other approved indications.	Although the curative intent of the use of rituximab in DLBCL makes the indication ostensibly different from other, chronic, uses of the medicine, the scientific principles of extrapolation still apply. A multicenter double-blind RCT of an investigational biosimilar rituximab candidate RTXM83 has reported noninferior efficacy and similar safety to the reference medicine in DLBCL.[45] The ongoing postapproval REFLECT study of Sandoz rituximab biosimilar in DLBCL has reported interim safety results with no unexpected safety signals.[46]
Recommendation 3	
Clinicians can expect similar outcomes in terms of efficacy, safety, and immunogenicity in a patient who is switched from the reference product to a biosimilar or between biosimilar brands.	Extensive evidence, including large-scale systematic reviews of clinical trials and real-world studies, is now available confirming that switching patients to a biosimilar from its reference medicine results in unchanged efficacy and safety trajectories.[47,48]
Recommendation 4	
With respect to use of biosimilars within a clinical trial, the trial protocol should provide clarity regarding acceptable options including stipulations on use of a specific brand, switching, and other relevant details required.	Expert Panel opinion found that removing the additional variable of different brand use would be preferable in the controlled setting of a clinical trial that is not specifically designed to compare such brands. This recommendation is made for simplicity of organizing and interpreting such clinical trials, and not due to any residual uncertainty about the similarity of registered biosimilar medicines.
Recommendation 5	
A biosimilar approved by the TGA is expected to have a similar physicochemical structure, biological activity, and an equivalent safety profile to the reference product. Therefore, it can be assumed that if a patient develops an adverse reaction to any brand of a biologic medicine, they would be likely to experience the same reaction to any other biosimilar brand. Switching to a biosimilar brand in a patient who experiences an AE that would require discontinuation of their existing biologic medicine is therefore not recommended. In certain circumstances, it may be possible and necessary to re-challenge a patient with a biologic medicine to which they have experienced a prior adverse event. Centers and hospitals should maintain protocols for such re-challenging. In this circumstance, it is reasonable that any biosimilar brand of the medicine could be used for the re-challenging.	There is a lack of evidence currently on the use of biosimilars in this context; however, Expert Panel opinion held that because biosimilars are considered therapeutically equivalent to their reference product, a biosimilar could be reasonably used in the same manner as the reference product.
Recommendation 6	
Clinicians should dose a biosimilar medicine and any concomitant medicines (chemotherapy and/or pre and post supportive medication) as they would with the reference product. No changes to dosing or other medications are required when switching a patient between products. Clinicians should refer to the appropriate product information and relevant guidelines for information on dose levels for particular medicines.	It is a requirement of approval that biosimilars have interchangeable dosing to their reference product.[17] Pivotal clinical trials for biosimilars are performed with the same concomitant medicines at the same doses in both the investigational (biosimilar) and control (reference medicine) arms of the trial.[7]

(Continues)

TABLE 2 (Continued)

Recommendation	Rationale
Recommendation 7	
Before initiation on a biosimilar medicine, patients should be made aware of the nonproprietary name of the medicine they will be receiving.Individual institutions should develop clear guidance as to: 1. Whether it is necessary that a patient is made aware that they are receiving a biosimilar. 2. The level of information about biosimilars that they receive. 3. Which HCP is primarily responsible for provision of this information. Detailed information and printable resources for consumers regarding biosimilar medicines can be found on the Australian Department of Health website: https://www1.health.gov.au/internet/main/publishing.nsf/content/biosimilar-awareness-initiative/	The level of information that a patient requires, as well as the person best placed to provide this information, will vary based upon a number of factors including patient factors, treatment factors, and the healthcare system/institution. The Expert Panel was therefore of the opinion that individual institutions are best placed to develop protocols for providing information for patients under their care. Patient information is highly important and the development of written guidance at the institution level to ensure appropriate information is provided was agreed to be preferable.
Recommendation 8A	
In the event that a hospital stocks multiple brands of a biologic medicine, hospital pharmacists and nursing staff should have a governance structure in place to ensure accuracy is maintained in labelling, dispensing, and administration of the drug, to avoid documentation errors and ensure traceability of which patient has received which brand(s).	The Expert Panel agreed that, due to the variation in hospital pharmacy systems across Australia, protocols governing the labeling, dispensing, and administration of biosimilar medicines should be introduced at the institution level.
Recommendation 8B	
If a hospital makes available multiple brands of a biologic medicine, hospital authorities should develop clear protocols on what their "default" brand of the medicine is. This should extend to third-party compounders who would require clear guidance on the brand required to be administered to patients.	The Expert Panel considered the situation in which multiple brands of a biologic are available within an institution, and found it unlikely that prescriptions will always specify the brand name to be prescribed. Therefore, a default brand at the institution level was felt necessary to avoid confusion between different stakeholders.
Recommendation 9	
As a result of practical realities, including drug and therapeutics committees or hospital governing bodies making decisions for local formularies and hospital pharmacies, the number of biosimilar brands a prescriber can select from may be limited. Decision-making bodies should consult with clinicians as part of their assessment process when considering biosimilar medicines used in hematology.	The Expert Panel felt that as clinicians retain the ultimate responsibility for their patient, they should be consulted as to which brands of a biosimilar medicine are made available for prescription.
Recommendation 10	
Pharmacovigilance processes for biologic medicines (including biosimilars) should be put in place at the hospital or health service level and adhered to by all healthcare professionals, for all biologic medicines.	The Expert Panel agreed that, as the introduction of biosimilar brands of medicines creates additional complexity in terms of tracking product names, manufacturers, and batch numbers, protocols should be developed at the institution level to ensure traceability of individual brands.

Extrapolation is a core tenet of the principle of biosimilarity, allowing biosimilars to offer cost reductions as a function of their more focused clinical trial program compared to the reference product.[7,36] It is also to ethically ensure a patient is not subjected to a clinical trial for which the outcome is already known.[7,37]

3.6 | "A"-flagging, substitution, and switching

Once approved by the TGA, a biosimilar medicine is assessed by the Pharmaceutical Benefits Advisory Committee (PBAC) for reimbursement through the PBS. As part of this decision, the PBAC may mark the biosimilar as "equivalent" to the reference product in the Schedule of Pharmaceutical Benefits, permitting the products to be substituted with one another at the point of dispensing at the pharmacy, a process known as "a"-flagging.[11,38]

The decision of whether to "a"-flag a biosimilar is made by the PBAC on a case-by-case basis on a number of factors, including[38]

a. The TGA determination of biosimilarity;
b. The availability of supportive data relating to the effects of switching between the reference product and the biosimilar product/s; and
c. Practical considerations relating to substitution by the pharmacist at the point of dispensing (eg, strength of formulation and number of units per pack).

For chemotherapy items prescribed and available under the Efficient Funding of Chemotherapy program, "a"-flagging is not required as they are already considered to be interchangeable. Reimbursement of these products is based on the most cost-efficient combination of vial sizes regardless of brand used.[39]

When a biosimilar is "a"-flagged, the prescribing physician can elect to tick the "brand substitution not permitted" box on the prescription, a measure intended to allow ultimate responsibility for the treatment decision to remain with the treating physician.[11,40] However, in a public hospital setting, the decision of which brand to dispense will be influenced by the brand(s) listed on the local or state formulary and stocked

within the hospital pharmacy or third party compounder. These are decided by local or state formulary committees and Drug and Therapeutic Use Committees, respectively.[41]

"Switching" in relation to biosimilars usually refers to the transition of a patient stable on one brand of a biologic medicine to a different brand of that medicine (eg, a patient who has previously received the reference medicine being "switched" to a biosimilar brand).[7,11,41] Switching to a biosimilar medicine is performed with the expectation of achieving similar clinical safety and efficacy outcomes to the reference brand, as well as to reduce treatment expenditure thereby assisting in the sustainability of the healthcare system. Switching and substitution are therefore related but independent concepts. Pharmacy substitution may or may not result in a switch in the patient's therapy, whereas switching can occur as a result of substitution or a determined effort from the prescribing physician.[11,41]

Based on the premise narrated in the section above, we have prepared a set of recommendations as tabulated in Table 2.

4 | RECOMMENDATIONS

Tabulated in Table 2.

5 | SUMMARY AND CONCLUSION

The availability and uptake of biosimilars in Australia represent an important component of the government's plans for a sustainable healthcare system.[19] Biosimilars provide similar therapeutic outcomes for patients while offering reduced costs and the potential for improved patient access to treatment.[20,21] This paper aimed to provide consensus recommendations to guide healthcare professionals in hematology on the use of these products as part of their clinical practice.

This publication presents various strengths—to our knowledge it is the first consensus statement publication presenting recommendations to Australian clinicians on biosimilar use in hematological disorders. Moreover, the recommendations presented were unanimously agreed upon by the expert panel, following the modified Delphi approach. Potential weaknesses include the lack of a new systematic review of literature; however, this is offset by the utilization of the review commissioned by the Department of Health,[8] and the lack of evidence grading of the recommendations.

The guiding principle of recommendations presented here is the establishment of therapeutic equivalence between a biosimilar and its reference medicine during its development and regulatory evaluation. This should provide confidence that an approved biosimilar can be used interchangeably with the reference medicine in any individual patient, across approved indications and settings, including both in patients naïve to the medicine and the "switching" of those stable on treatment. Nevertheless, there are practical and administrative considerations associated with biosimilar introduction that should be addressed at the institutional level, to ensure traceability of the product being dispensed and to optimize patient outcomes.

We hope that the information and recommendations presented here will serve to reassure clinicians on the appropriate use of biosimilar medicines, and to encourage the implementation of local processes to continue to incorporate biosimilars into the care of Australian hematology patients. We also hope that this article sparks further discussion of the topics contained within and is followed by guidelines and protocols generated by professional societies and individual institutions.

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CONFLICTS OF INTEREST

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Dr Gareth Gregory's institution receives research funding from Abbvie, Amgen, Bristol-Myers Squibb, Astra Zeneca, Beigene, Celgene, Merck Sharpe & Dohme, Pharmacyclics, Janssen-Cilag, and Roche; he is an advisory board member to Roche/Genentech, Janssen-Cilag, Gilead, and Sandoz/Novaritis; speakers bureau to Roche/Genentech, Gilead; and received travel expenses from Roche/Genentech.

Dr Christine Carrington is a past member of Sandoz advisory board and has received educational funding from Merck Sharpe & Dohme.

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Dr Ian Irving has in the last 2 years been part of advisory boards for Amgen, Janssen, and Sandoz; received speaker honorarium from Amgen; and is a shareholder in Icon Group, which provides pharmacy and drug compounding services.

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AUTHOR CONTRIBUTIONS

All authors contributed significantly to discussions at the Expert Panel meetings, and were involved in drafting, review, and final approval of the manuscript.

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