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Governance of biologics in SA Health facilities Clinical Guideline

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Government of South Australia
SA Health

Contents

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1. Introduction

This guideline provides Local Health Networks (LHNs), state-wide services and SA Health employees with guidance for good governance and clinical decision-making in relation to use of biologics in SA Health facilities.

2. Executive Summary

Biologics are medicines whose active substance has a large, complex, molecular structure, which can only be made by or derived from a living organism (e.g. bacterium, yeast, human/animal cell line).(1) Biologics vary in complexity from small, highly purified proteins to more complex structures such as monoclonal antibodies.

- **Governance**

  Governance of medicines in hospitals requires that all biologics are managed in an appropriate manner that is the same as any other medicine. Decision-making and medicines management processes should be transparent and accountable, based on robust evidence of safety, efficacy and cost-effectiveness according to SA Health policy.

- **Reference biologics and their biosimilars**

  Biologics are important in the management of many conditions. Following the patent expiry of a medicine, additional pharmaceutical manufacturers can produce and market that medicine, which results in price competition between manufacturers. Biologics are important in the management of many conditions but often come at significant financial cost.

  Within this document the term biologic is used broadly to encompass both the reference product and their biosimilars.

  - Biosimilars are highly similar versions of the reference biologic. Each biologic is unique and cannot be considered as bioequivalent.
  - A biosimilar may be switched with the reference biologic where it has been evaluated by the Therapeutic Goods Administration (TGA) for therapeutic equivalence and demonstrated to be highly similar with the reference product.(2)

    The Pharmaceutical Benefits Advisory Committee (PBAC) makes recommendations about the substitutability of brands on the Pharmaceutical Benefits Scheme (PBS) based on TGA advice on therapeutic equivalence.

- **The use of biologics in SA Health facilities**
  - The SA Health Medicines Formulary (the Formulary) lists all biologics medicines (including formulations, strengths and indications) approved for use in SA Health facilities.
  - The SA Formulary Committee (SAFC) or SA Medicines Evaluation Panel (SAMEP) are responsible for evaluating and recommending all medicines including biologics for inclusion on the Formulary.

- **Initiating biologics in treatment-naive patients**
  - When initiating biologic therapy for an approved indication all treatment naïve patients should be commenced on the biologic approved by the SAFC (or SAMEP).
  - Treatment with another biologic should only be considered after patient response to the first line biologic product has been assessed as not clinically appropriate.

- **Switching and substitution in SA Health facilities**
  - Switching will only occur if the TGA have approved the products as able to be switched, and the switch is part of a SAFC or SAMEP approved switching program.
  - Substitution will only occur if the PBS has assessed and approved the products as substitutable; and the substitution has been approved by the SAFC or SAMEP.
- **Admitted patients and ongoing biologic treatment**
  - As a general principle, patients requiring ongoing biologic treatment during an admission to a SA Health facility will receive the Formulary listed brand for the relevant indication if the patient's usual brand of biologic and the Formulary listed brand have been deemed suitable for switching based on TGA and PBS recommendations
  - Patients' own medicines should be considered for use if appropriate in accordance with the Patients' Own Medications Policy
  - Switching to the Formulary brand of biologic for admitted patients with ongoing biologic treatment should take into consideration the presentation of the biologic, including its administration device, and the impact any change may have on the patient.
- **Medicines documentation and communication**
  - Across all aspects of a patient's healthcare journey, the appropriate and safe documentation and communication of biological medicines should be ensured, including active ingredient and, where appropriate brand name (adhering to the principles of active ingredient prescribing). This includes medication histories, medication reconciliation documents, medication charts, administration lists, prescriptions, medication lists for patients, discharge summaries, or any other transition of care documentation.
- **Patient Engagement**
  - Patients should be actively engaged in shared decision making when considering and receiving treatment with biologics, including when considering switching biologic brands.
  - Patient education should be provided to promote patient understanding.
  - Patients should be familiar with their biologic's active ingredient and brand name to avoid inadvertent switching.
- **Pharmacovigilance**

  Pharmacovigilance is particularly important in the use of any biologic. LHNs and state-wide services should have processes in place to support effective identification and traceability of biologics at all stages of patient care.

Refer to the background and general section for further detail.

3. Background

Biologics provide highly specific and targeted therapy, in the management of many conditions, including rare or severe or chronic diseases but often come at significant financial cost. Following the patent expiry of a biologic, additional pharmaceutical manufacturers are able to produce and market that medicine, which with price competition between manufacturers, results in a reduction in the medicine price.(3)

The availability of biosimilars in Australia has significantly decreased the cost of individual biologics and consequently could potentially:

- improve cost-effectiveness of biologics in various conditions,
- improve economic efficiencies,
- expand access to medicines via broader patient eligibility or broadening of approved and/or subsidised indications.

Medicines governance/oversight bodies and health professionals directly involved in the medicine management pathway need to carefully consider the clinical evidence, opportunities and risks associated with the introduction of biosimilars into clinical practice.

Biologics are inherently complex molecules, or mixtures of molecules. This complexity is a result of characteristics such as large molecular size, structure and post-translational modifications such as glycosylation.(1) These medicines are produced with the use of a living system (such as a microorganism or an animal cell line) with complex manufacturing processes and protocols, which are the proprietary information of the originator company. Although there is some within-product micro-heterogeneity, these variations are well-understood and controlled by the manufacturers.(3, 4)

Biosimilars

The regulatory evaluation of biosimilars reflects the molecular complexity of biologics and the nature of their production process. A manufacturer of a biosimilar medicine must demonstrate the comparability of their product with the reference biologic. The TGA has adopted a totality of evidence approach to the regulatory evaluation of biosimilars in Australia. This totality of evidence approach takes into account detailed analytical comparison to the reference product in terms of:

- physicochemical characterisation – molecular structures and critical quality attributes (e.g. glycosylation);
- preclinical and clinical pharmacokinetic and pharmacodynamic data (e.g. in-vitro pharmacology, pharmacokinetics [phase I studies]); and
- clinical trials including clinical efficacy, safety and immunogenicity evidence (specifically designed phase III studies with pre-defined equivalence criteria based upon sensitive clinical endpoints).(3, 4)

The process for evaluating biosimilars is described in the April 2018 TGA document, *Biosimilar medicines regulation*, version 2.2.(5)

The evaluation of biosimilars does not replicate the full range of studies that were conducted during the development of the reference product. Instead, the evaluation aims to demonstrate that there are no meaningful differences between the reference product and the biosimilar, such that the experience with the reference product can be reasonably applied to the biosimilar. On this basis, a biosimilar may be approved for indications, consistent with those of the reference product and which may be additional to those in which comparability studies were conducted; this is known as extrapolation of indications.(3)

The TGA approach to extrapolation of indications has been adopted from the European Medicines Agency (EMA) Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, which states:

" The reference medicinal product may have more than one therapeutic indication. When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable but needs to be scientifically justified. In case it is unclear whether the safety and efficacy confirmed in one indication would be relevant for another indication, additional data will be required. Extrapolation should be considered in the light of the totality of data, i.e., quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physicochemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication."(6)

To date, evidence in the literature, including clinical trials and real-world studies across multiple different biologics and their biosimilars, demonstrates that similar outcomes can be expected in terms of efficacy, safety, and immunogenicity in a patient who is switched from the reference product to a biosimilar or between biosimilar brands.(3, 7-10)

4. Definitions

- **"a' flagging**: means the PBAC has determined a biosimilar is substitutable with its reference biologic on the PBS, as indicated by ' a' immediately before the brand names of a particular strength of an item. This follows acceptance by the TGA of evidence submitted by the sponsor of the biosimilar demonstrates the two products are either bioequivalent or therapeutically equivalent, or that justification for bioequivalence or therapeutic equivalence data is not required. In these circumstances it is expected that these brands may be substituted without the recipient experiencing differences in clinical effect.
- **Biologic:** means a medicine whose active substance has a large, complex, molecular structure, which can only be made by or derived from a living organism (e.g. bacterium, yeast, human/animal cell line).(1) Biologics vary in complexity from small, highly purified proteins to more complex structures such as monoclonal antibodies. Biologics are also referred to as biological medicines.

  Biologics include:

  - peptide hormones and glycoproteins (e.g., insulin, human growth hormone, follitropin, filgrastim)
  - immunological medicines (e.g., monoclonal antibodies and vaccines)
  - other biological products, including polysaccharides (e.g. low molecular weight heparins).(5, 11)

  Within this document, the term biologic is used broadly to encompass both the reference product and their biosimilars.
- **Reference biologic:** means a biologic that is registered in Australia and where that registration was based upon a full regulatory evaluation of quality, safety and efficacy data. This product is the first brand of that biologic available and as such may be referred to as the originator or innovator.
- **Biosimilar:** means a highly similar version of an already registered reference biologic produced by an additional manufacturer that:

  - has been demonstrated to be highly similar in physicochemical, biological and immunological characteristics, efficacy and safety, based on comprehensive comparability studies with the reference product(12), and

  has been evaluated by the Therapeutic Goods Administration (TGA)(5) according to its guidelines and other relevant European Union (EU) guidelines adopted by the TGA.(5) biosimilar can as be known as similar biological medicinal product [EU]; similar biotherapeutic product [WHO]; subsequent entry products [Canada]).(5, 13)

- **Efficient Funding of Chemotherapy (EFC):** Under the PBS EFC arrangements for cytotoxic chemotherapy (administered by infusion or injection) brand substitution of chemotherapy medicines may be undertaken by pharmacists at the point of dispensing when patients agree to the substitution and the prescriber has not indicated on the prescription form that substitution should not occur. These medicines are not 'a' flagged in the PBS.(12, 14)
- **Pharmacovigilance:** means the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
- **Substitution:** the practice of dispensing one brand of a biologic instead of the prescribed brand of the biologic when those brands have been endorsed as equivalent and substitutable by an appropriate body e.g., Pharmaceutical Benefits Advisory Committee. Substitutable medicines are marked in the Schedule of Pharmaceutical Benefits with an 'a' (a-flagged). Brand substitution by pharmacists is permitted without reference to the prescriber when the patient agrees to substitution and the prescriber has not indicated on the prescription form that 'brand substitution not permitted'.
- **Switching:** changing between two brands of the same medicines. This could be changing from the reference biologic to biosimilar, or vice-versa or between biosimilars.

5. Principles of the standards

The following National Safety and Quality Health Service Standards apply:

- **Standard 1 – Governance for Safety and Quality in Health Care**
- **Standard 2 - Partnering with Consumers Standard**
- **Standard 4 – Medication Safety**

6. General

6.1 Governance

Governance of medicines in hospitals requires that all biologics are managed in an appropriate manner that is the same as any other medicine. Decision-making and medicines management processes should be transparent and accountable, and based on evidence of safety, efficacy and cost-effectiveness according to SA Health policies and guidelines.

6.1.1 Initiating biologic therapy in treatment naive patients

- All treatment-naïve patients will be started on the Formulary first line biologic recommended for the indication.
- In order to optimise efficient resource utilisation and equity of access, biologics are tendered competitively on a state-wide level. As the stimulation of antibody production in patients by biologics is highly unpredictable with current technologies, it would not be possible to determine which biologic a patient will have optimal response to. Therefore, all patients should be commenced and evaluated on the biologic listed as first line therapy on the Formulary for the indication before a clinical assessment is made to determine ongoing use/efficacy. Second line biologic treatment options may not be listed on the Formulary, but available via the individual patient use (IPU) application process.
- Use of biologics for non-TGA approved indications (unregistered/off-label)

As with other medicines considered for inclusion on the Formulary a biologic that has not been approved by the TGA for a specific indication or sub-population, will be assessed by the SAFC or SAMEP in terms of safety, efficacy and cost-effectiveness.

More information on the Formulary and the IPU process can be found on SA Medicines Formulary page.

6.1.2 Switching

- Switching between biologics should be in accordance with the SAFC or SAMEP approved switching program and in compliance with the preferred Formulary listing.
- To prevent inadvertent switches, support consistency and monitoring of care frequent (multiple) switching between biologics should be avoided.
- Due to the potentially different immunological profiles of biologics, the decision to switch a patient who has already received therapy with a specific biologic to another requires appropriate clinical input and monitoring.
- Treating clinicians may request to switch a patient's biologic if clinically indicated.
- Patients should be informed of any changes to their therapy to avoid confusion and prevent any inadvertent switches. As with any treatment decisions patients should be actively engaged in shared decision making when considering and receiving treatment with biologics, including biologic switching.

6.1.2.1 Admitted patients and ongoing treatment

- As a general principle, patients requiring ongoing biologic treatment during an admission to a SA Health facility will receive the Formulary listed brand for the relevant indication, if the patient's usual brand of biologic and the Formulary listed brand have been deemed suitable for switching based on TGA and PBS recommendations .
- Patients' own medicines should be considered for use if appropriate in accordance with the Patients' Own Medications Policy
- Switching to the Formulary brand of biologic for admitted patients with ongoing biologic treatment should take into consideration the presentation of the biologic, including its administration device, and the impact any change may have on the patient. In certain circumstances, it may not be appropriate to switch to the Formulary listed brand, e.g. length of admission, medication safety issues such as the use of brand-specific administration devices; minimising the risk of patient confusion.
- Patients should be actively engaged in shared decision making when considering switching biologic brand.
- Where switching occurs, there should be appropriate documentation and communication of the switch with patients and their health practitioners. Appropriate information and education with regard to administration devices should accompany consideration and supply of the biologic.

6.2 Medicines documentation and communication

Across all aspects of a patient's healthcare journey, the appropriate and safe documentation and communication of biological medicines should be ensured, including active ingredient and, where appropriate brand name (adhering to the principles of active ingredient prescribing).

- To reduce confusion, avoid inadvertent switches, support consistency and monitoring of care, where appropriate, a prescriber may include a brand name, in addition to the active ingredient name for clinical reasons and/or patient safety.(15)
- For dispensing, administration and medicine governance, both the active ingredient and brand name of the biologic, should be documented across a patient's healthcare journey.(3)
- For compliance with legislation (16) and principles of active ingredient prescribing, the prescription must include active ingredient(s), unless the biologic medicine is included in the list of excluded medicinal items or list of medicines for brand consideration. (15) Electronic systems programs used to generate PBS/RPBS prescriptions must not apply the brand to prescriptions by default.(17)

6.3 Patient engagement

- As for any medicine, it is important for patients to be fully informed about decisions and choices when receiving treatment with a biologic. Patients should be actively engaged in shared decision making regarding biologic treatment.
- Patients should be advised about therapeutic options, safety, benefits and potential harms, and differences between treatments. Information provided to the patient about potential adverse reactions associated with treatment will facilitate partnerships between patients and clinicians in the monitoring for adverse reactions and implementation of adverse risk mitigation strategies.
- Appropriate education and information should be provided, including education regarding administration devices. Written information, e.g. the Consumer Medicine Information (CMI) leaflet, should be available to promote patient understanding.

6.4 Pharmacovigilance

- Pharmacovigilance is particularly important in the use of any biologic. LHNs and state-wide services should have processes in place to support effective identification and traceability of biologics at all stages of patient care, including dispensing, administration, documentation of any adverse effects (or suspected adverse effects) as well as procurement and storage.(3)
- Where possible the brand name and batch numbers of biologics should be recorded to assist the traceability of the biologic in the event of an adverse event.(3)
- Health professionals, patients and the pharmaceutical industry have a shared responsibility to monitor outcomes and identify, monitor and report any adverse effects or unexpected adverse effects, through the TGA online adverse event management system and local systems, e.g. the SA Health Safety Learning System (SLS).
- In some circumstances LHNs and state-wide services may need to manage stock of multiple brands of a biologic, e.g. in contract transition periods. Processes should be put in place to avoid inadvertent switches, documentation errors and ensure traceability regarding the brand(s) a patient has received.(3)

7. Safety, quality and risk management

National Safety and Quality Health Service Standards

National Standard 1 Clinical Governance	National Standard 2 Partnering with Consumers	National Standard 3 Preventing & Controlling Healthcare-Associated Infection	National Standard 4 Medication Safety	National Standard 5 Comprehensive Care	National Standard 6 Communicating for Safety	National Standard 7 Blood Management	National Standard 8 Recognising & Responding to Acute Deterioration
☒	☒	☐	☒	☐	☐	☐	☐

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SA Health Supporting Documents

- South Australian Medicines Formulary (Establishment and Maintenance) Framework
- TGA Evaluation of biosimilars
- TGA Biosimilar medicines regulation
- Statewide Formulary for High Cost Medicines Policy Directive
- High Risk Medicines Management Policy Guideline
- Patients' Own Medications Policy

9. Document Ownership and History

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