

ISOPP Global Position on the Use of Biosimilars in Cancer Treatment and Supportive Care

Introduction

With the development of innovative cancer treatments over recent decades, the cost of cancer care has risen exponentially,¹ limiting patient access to patented originator biotherapeutics in many countries. The introduction of biosimilars to the market has created new opportunities as well the need for changes in practice within healthcare institutions. A “biosimilar” ^[T³] is a biotherapeutic product ^[T⁴] which is highly similar in terms of quality, safety and efficacy to an already licensed originator product.^{2,3,4} Across nations, the advent of biosimilars has increased access to care by generating significant price competition and a mechanism for healthcare institutions to contain costs, with most biosimilars entering the market priced at least 30% lower than the reference product.⁵ A survey conducted in May 2019 by the International Society of Oncology Pharmacy Practitioners (ISOPP) with 90 oncology pharmacist ^[T⁹] respondents from 27 countries worldwide found 93% of respondents in 26 of the represented countries were employed within institutions currently using, or planning to use, biosimilars in practice.⁶ Medicine pricing was cited as the most common factor influencing the decision to use biosimilars worldwide. Many of the available biosimilars are indicated for oncology or supportive care indications, with several biosimilar versions of six originator biotherapeutics ^[T¹⁰] approved for use in pharmaceutical markets around the world. Furthermore, several patents for originator biotherapeutics used in oncology have recently expired or are anticipated to expire in the coming years in the United States and Europe,⁷ indicating future growth and continued expansion of biosimilar use in the oncology setting.

Although biosimilars lack clinically meaningful differences in therapeutic activity as compared to the originator product, these complex biological molecules are not considered identical chemical copies, unlike generics, and minor differences in molecular structure and inactive compounds may exist.^{2,3,4} A thorough understanding of these differences and their clinical implications is necessary for optimising medicines-use practices involving biosimilars. ISOPP believes that training and education are paramount to ensure the safe and effective use of biosimilars within healthcare institutions. This position statement, developed by the ISOPP Biosimilars Taskforce, aims to provide the global oncology pharmacy community with guidance to support decisions around biosimilar use. The 11 statements cover the regulation and evaluation of biosimilars, practical issues around local implementation, the education of healthcare staff and patients, and the requirement for ongoing pharmacovigilance ^[T¹¹] and outcome monitoring.

Role of the Oncology Pharmacist

Biotherapeutic and biosimilar products possess a great deal of heterogeneity with regards to manufacturing, purity, stability and immunogenicity. Oncology pharmacists with an understanding of these complexities and the ability to assess available comparability data between products play a crucial role in the multidisciplinary effort to evaluate and implement biosimilar use within healthcare institutions. Additionally, oncology pharmacists are well positioned to act as resources for staff and patient education regarding the safety and efficacy of biosimilars as compared to originator products. Prescriber reluctance to accept biosimilars as

Table 1 lists definitions of commonly used terms throughout this article [referred to using T1, T2, T3, etc.].

therapeutic equivalents to originator biotherapeutics is cited as a common barrier to biosimilar implementation within healthcare institutions across the globe.⁶ Oncology pharmacists are ideally placed to educate prescribers on the regulatory requirements and testing involved in the licensing and marketing of a biosimilar.

Oncology pharmacists should serve as institutional leaders for biosimilar implementation by conducting formulary reviews within pharmacy and therapeutics committees or by being involved in other interdisciplinary groups responsible for medicines use. They also ensure optimal prescribing through management of paper and electronic treatment plans, and should routinely conduct pharmacovigilance monitoring post implementation. By conducting observational and/or retrospective research and medicines-use analysis at local and national levels, oncology pharmacists can help influence institutional, regional or national policies surrounding biosimilar use and implementation. Because of their unique skill set, oncology pharmacists can play a crucial role in the optimisation of medicines-use processes surrounding biosimilars.

Statement 1: A biosimilar licensed via national or regional regulatory agencies requiring rigorous pathways for medicine manufacturing and evaluation is considered therapeutically equivalent to the originator biotherapeutic. However, a biosimilar is not considered therapeutically equivalent to other biosimilars of the same originator biotherapeutic.

- Internationally-recognised regulatory bodies, such as the European Medicines Agency (EMA), the World Health Organization (WHO), and the Food and Drug Administration (FDA), have established pathways and guidelines for manufacturing companies to follow for biosimilar development and licensure.^{2,3,4} These pathways require rigorous pharmacokinetic and pharmacodynamic comparability studies between the developed biosimilar and the originator biotherapeutic, and medicines licensed by way of these strict criteria are considered therapeutically equivalent to the originator biotherapeutic. Several other agencies exist that are known to have similar standards for biosimilar marketing and approval and include, but may not be limited to, the Therapeutic Goods Administration (TGA) of Australia, Health Canada, the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan and the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom. Medicines licensed in countries as intended copies of the originator, but which are without the same quality of comparability data, or where manufacturers have otherwise followed less stringent agency-approval criteria, **should not be used**. Such products are known as non-comparable biotherapeutics or “biomimics” [T2].⁸ The safety and efficacy of these products compared to the originator biotherapeutic are unknown. ISOPP does NOT support or recommend the use of biomimics in practice, and oncology pharmacists practicing in countries that operate under medicine licensing agencies that do not strictly regulate the introduction of biosimilars to the market should avoid using these products.
- A biosimilar is not considered equivalent to other biosimilars of the same originator biotherapeutic; therefore, each biosimilar product should be evaluated individually against the originator.

Statement 2: Biosimilars are not considered interchangeable with originator biotherapeutics and should not be automatically substituted. However, a switchover from an originator biotherapeutic to a biosimilar within institutions or for individual patients is acceptable and encouraged.

- Interchangeability ^[7] is often linked to automatic substitution, ^[19] a practice that is common for generics, or chemical clones, of brand-name medicines. Biosimilars, however, are not chemical clones of originator biotherapeutics. Instead, these medicines are formulated individually using their own unique biological process and must undergo pharmacokinetic and pharmacodynamic testing against the originator biotherapeutic to be deemed a biosimilar product.¹⁰ Interchangeable products must demonstrate that the same clinical result can be expected in any given patient, and that efficacy and safety are not significantly different as a result of alternating or switching ^[13] products. Currently, the only regulatory agency with the facility to assign an “interchangeable” designation to a biosimilar is the FDA. That said, the FDA has not deemed any biosimilar interchangeable with an originator biotherapeutic at this time. Despite this, individual countries and states operating under the regulations set forth by medicine licensing agencies may create their own laws governing automatic substitution.^{9,11} Globally, biosimilar automatic substitution has not been universally adopted, with many countries operating under local regulatory agencies that provide minimal to no guidance regarding biosimilar use. Furthermore, most states in the United States and many countries in the European Union have chosen to restrict or prohibit automatic substitution by pharmacists. Given the possible risks associated with transitioning between biotherapeutic products and the absence of an interchangeability designation, automatic substitution with biosimilars is discouraged. Collaborative efforts, such as formulary addition or the development of treatment protocols, to select an institutionally-preferred agent and to switch from originator to biosimilar product are strongly encouraged as methods to facilitate biosimilar use. However, although situations may occur when switching between biosimilars of the same originator product is necessary for tolerability or financial reasons, repeatedly swapping biosimilars for an individual patient is discouraged and should be avoided where possible.

Statement 3: Extrapolation of biosimilar data to all clinical indications may occur provided that enough relevant safety and efficacy data exist to support use.

- Extrapolation ^[5] is an important concept related to biosimilars, and allows for the approval and use of a biosimilar for an indication carried by the originator biotherapeutic, but not studied in clinical trials by the biosimilar.^{2,3,4} In order for biosimilar use to be extrapolated to indications studied only in the originator product, the totality of evidence demonstrating similarity between the biosimilar and the originator must be considered, which encompasses more than just available clinical trial data and includes other comparison data such as structural, physiochemical, functional and other non-clinical data.^{12,13} In order for data to support extrapolation, indications should have the same molecular mechanism of action, involve the same receptor type, location and expression, and have similar binding, dose response and patterns of molecular signaling upon target binding. Furthermore, to ensure no additional safety concerns are present for a given indication with a biosimilar over the originator, characterization of safety, immunogenicity ^[6] and pharmacokinetic biodistribution must be present among the totality of evidence.^{1,3,12,14} Although regulatory agencies must consider this information to make judgments regarding extrapolation prior to approval, this information should also be considered by healthcare institutions, without commercial bias, when making judgments about the use of biosimilars outside of their licensed indications or outside of the licensed indications for the originator (off-label use ^[8]).

Statement 4: Differences between originator and biosimilar product formulations do not alter clinical efficacy, but may enhance immunogenicity or intolerability risks. Inactive components should be reviewed for each biosimilar product before use.

- In addition to molecular differences between a biosimilar and its originator product, differences may exist in excipients or inactive ingredients contained within formulations to maintain product stability and integrity. These differences are not intended to alter clinical efficacy, but may contribute to patient intolerability or sensitivity, or an increase in immunogenicity.¹⁶ Immunogenicity testing has been an integral component of biosimilar clinical trials and continues to be an area of emphasis in ongoing pharmacovigilance.¹⁵ Currently, there are expectations from the FDA and other medicine licensing agencies for biosimilar manufacturers to gather long-term safety data for these products.¹⁷ Stability data must be obtained for each marketed biosimilar product and evaluated against the originator product in order to make informed medicines-use decisions.

Statement 5: Partial implementation of a biosimilar, or institutional use of multiple biosimilars, may need to be considered as appropriate for the healthcare institution or patient populations served.

- To support timely implementation of approved biosimilars when there are financial barriers and/or clinical issues preventing full implementation, it may be necessary to partially implement a biosimilar within an institution for a given patient population. Such partial implementation would require the procurement of both the original biotherapeutic and one or more biosimilar products. As an example, if there are concerns regarding data extrapolation for a biosimilar in a particular indication where licensing has only been obtained by the originator biotherapeutic, an institution may decide to keep individuals with this indication on the originator product, while switching other patients to the biosimilar. As another example, if there is a lack of interchangeability data between a biosimilar and an originator biotherapeutic, an institution may decide to switch to a biosimilar for use in patients newly starting therapy, while maintaining the originator biotherapeutic for patients continuing with this therapy. Consistent with this example, minimal to no data may be available on the interchangeability between multiple biosimilars, which may further contribute to partial implementation.¹⁸ Lastly, patient convenience associated with the use of an originator product may not be transferable to a biosimilar due to differences in administration or presentation, limiting full biosimilar implementation. Some examples of when convenience currently lies with the originator biotherapeutic include the pegfilgrastim on-body injection device, subcutaneous rituximab or trastuzumab products and accelerated infusion protocols associated with originator rituximab. To summarise, when there is a clinical issue making a clear choice uncertain, partial implementation may be necessary for patient / clinician confidence until more information on a specific product or disease state becomes available. Medicine shortages and, in some countries, the healthcare reimbursement environment (specific payer rules or preferences), may also necessitate the need for partial implementation within institutions.¹⁹

Statement 6: Adherence to best practice guidelines on the storage and labeling of biosimilar products will reduce the risk of selection error. In the absence of best practice guidelines, universal naming guidelines should be applied to support biosimilar tracking and pharmacovigilance.

- Where there may be a need for partial biosimilar implementation, institutions may be in a position of having to use or carry multiple brands of a biotherapeutic (biosimilar and/or originator or additional biosimilar). Biosimilar products are marketed with the same generic name stem as the originator products, but each also has its own brand name, with some regulatory bodies requiring a unique 4-letter suffix to follow the stem. Given the need for product administration transparency, use of available best practice guidelines to guide product storage and nomenclature within the medical record and on labeled compounded products is encouraged for appropriate product identification.²⁰ In countries where there are no guidelines, ISOPP recommends that biosimilars and originator biotherapeutics be identified on the medicine label and in the medical record using two identifiers - the generic name stem and either the brand name or the 4-letter suffix. Labeling should be congruent worldwide, supporting global interchange and distribution of products, but also providing the transparency and clarity needed to support efficacy and pharmacovigilance follow-up activities if a patient is treated in multiple institutions or countries.^{21,22} When keeping both biosimilar and originator products, or multiple biosimilar products, in stock, all similarly-named products should be physically segregated and clearly labeled to prevent unintended product selection. Where available, consideration should be given to the adoption of barcode scanning technology to prevent selection error.

Statement 7: Multidisciplinary groups should guide the safe, effective and fiscally appropriate institutional use of biosimilars.

- The decision to use a biosimilar is a clinical partnership between medical providers, nurses, pharmacists, financial administrators and other applicable regulatory personnel. Prior to implementation, each product should be evaluated by a multidisciplinary committee that takes into account clinical effectiveness, pharmaceutical and administration details, safety and cost in order to minimize bias in decision making. Key findings of new or recent studies and changes in regulatory policies and processes should be shared with this committee on a regular basis to facilitate group understanding and shared accountability.¹⁵ This committee would benefit from education regarding pharmacology, clinical and safety information and best practices around documentation and billing practices.

Statement 8: Staff education on biosimilars should reference published, evidence-based and peer-reviewed literature whenever possible. Educational materials should be updated and reviewed on an ongoing basis.

- To optimise use of a biosimilar, clinicians and staff require education on available data comparing the safety and efficacy of the biosimilar to the originator product. This information should reference published, evidenced-based and peer-reviewed data wherever possible. In addition, general biosimilar education should be provided which includes patient, organisational and societal benefits of the use of these agents and also the regulatory criteria for market approval. Areas requiring special emphasis include data extrapolation, interchangeability differences between switching and automatically substituting products, and differences between biosimilars and originator biotherapeutics that may contribute to enhanced risk of immune or other adverse reactions.^{15,23} Furthermore, education on product drift [^{T12}] that results in differences between batches of originator biotherapeutic, similar to

those found between biosimilars and originator biotherapeutics, may strengthen support for biosimilar use amongst clinicians.²¹ Clinicians should be provided with additional information detailing common methods of disinformation around biosimilars and methods for examination of such information to offset potential negative detailing in a competitive marketplace. Staff education should be ongoing in an effort to confirm or clarify existing information and to update clinicians on new clinical and regulatory information.^{15,17}

Statement 9: Patients should be educated about biosimilars with resources that are evidence-based and tailored to patient demographics and health literacy. Such resources should be publicly available and adaptable to reflect the target population's needs.

- Given the high level of brand awareness in the public, patients who are resistant to generic medicine use may likewise be hesitant to adopt biosimilars. To facilitate acceptance of biosimilar use, patients require education on the clinical similarities and differences between a biosimilar and its originator biotherapeutic, and on the health and economic benefits of biosimilar use.²¹ Patients should also be made aware of biosimilar support services and publicly available education materials.¹⁹ Use of available, standardised and evidence-based educational materials from professional societies, government groups and patient advocacy groups on biosimilars promotes a better understanding of biosimilars among patients.¹⁷
- In countries or locations where public organisations are not yet providing educational materials, they should be obtained from product manufacturers, medicine licensing agencies (e.g. the FDA²⁴ and the EMA^{25,26}), national and international healthcare organizations (e.g. the National Health Service or RM Partners Vanguard²⁷) and patient support organization websites (e.g. Lymphoma Action: www.lymphoma-action.org.uk²⁸). Educational materials may need to be translated into local languages or otherwise altered to meet patient care needs, such as health literacy levels.

Statement 10: Institutional cost savings made through the use of biosimilars should be used to keep patient costs manageable and to stabilise budgets in order to maximise the number of patients served.

- Globally, government and institutional pressures exist to optimise the use of available resources and healthcare budgets at a time of rapid expansion in the pharmaceutical market. The savings achieved by the adoption of biosimilars could offset the impact of new and expensive medicines on total formulary costs as they enter the market or change standards of care. The timely adoption of biosimilars upon availability would maximise these savings. When a suitable biosimilar has been identified for use by the pharmacy and therapeutics committees, a planned implementation strategy must be put into place, with input from all stakeholders, to ensure an efficient and successful introduction to practice. For successful conversion to a biosimilar, education of clinicians and patients on both the financial and clinical impacts of biosimilar implementation is crucial. While the financial benefits of implementing biosimilars are a key factor, it is equally important to highlight that conversion to a biosimilar does not diminish care quality.²¹

Statement 11: Pharmacovigilance and patient-outcome monitoring are integral to the safe and effective use of biosimilars in different populations and indications.

- Current evidence indicates that biosimilars are generally safe, well tolerated and effective, with the primary concern over their use being that of immunogenicity. At present, there is no evidence that the use of biosimilars, when personalized for the needs of each patient, confers a higher risk of clinical adverse effects, hypersensitivity reactions or neutralizing antibodies than the originator product.²⁹ That said, the safe use of biosimilars is an area of uncertainty amongst many clinicians. Ongoing patient-outcome monitoring and pharmacovigilance are necessary for the collection of real-world evidence that provides clinician reassurance and contributes to the relevant body of literature.²¹ Patient characteristics and regulations for medicines approval and automatic substitution vary throughout the world, making data comparisons challenging, and thus careful evaluation and comparison of published real-world data are necessary to determine applicability.²³ Continued development of post-marketing evidence is integral to the affirmation of biosimilars, serving to increase patient and clinician confidence. Practicing pharmacists should contribute to the evidence through audits and research as well as documentation and reporting of any notable adverse events with biosimilar or originator products through the WHO and national regulatory bodies.¹⁷

Summary

The introduction of biosimilars to the pharmaceutical market has provided healthcare institutions with new cost-saving opportunities. However, their implementation poses a set of challenges, which varies across nations. These challenges may include the absence of government regulations guiding biosimilar use, difficulties with the interpretation and extrapolation of clinical data, the lack of education of patients and clinicians, and the need for ongoing pharmacovigilance and post-implementation monitoring. ISOPP is committed to supporting the use of biosimilars. These Standards have been developed to assist institutions to introduce biosimilars into their practice safely and successfully.



ISOPP Biosimilars Taskforce Members

Joseph Bubalo, United States

Alex Chan, Singapore

Milagros Cubilla, Panama

Mário De Lemos, Canada

Harbans Dhillon, Malaysia

Emma Foreman, United Kingdom

Morgan Frazer (Smith), United States

Jatinder Harchowal, United Kingdom

Nirachorn Kuchonthara, Thailand

Annemeri Livinalli, Brazil

Rodrigo Macedo, Brazil

Winnie Mwangi, Kenya

Hisanaga Nomura, Japan

Shaun O'Connor, Australia

Himanshu Patel, Canada

Margaret Patterson, Australia

Jim Siderov, Australia

Mayde Seadi Torriani, Brazil

Barbara Yim, United States

Table 1: Terms and Definitions

Term	Definition
T1 Automatic substitution	The practice by which a pharmacist is obliged, without the need for provider approval, to dispense an equivalent and interchangeable drug in accordance with local and/or national regulations.
T2 Biomimics (also known as ‘Non-comparable biotherapeutics’)	Intended replica medicines of biotherapeutic products that do not meet regulatory requirements of biosimilarity to the originator biotherapeutic product. Such requirements include comparability studies, safety analyses and other tests as stipulated by the relevant health regulatory bodies.
T3 Biosimilar	A medicinal product containing a highly similar version of the active substance of its originator or reference product (biologic), derived from living organisms. Biosimilar products include hormones, small proteins, vaccines, fusion proteins and monoclonal antibodies. A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing approved reference product.
T4 Biotherapeutic product (also known as ‘biologic’, or ‘biotherapy’)	A medicinal product derived from a living organism in cell culture and produced using biological means such as recombinant DNA technology. Examples include monoclonal antibodies, interferons, interleukins, cytokines and growth factors as well as products from novel cell lines.
T5 Extrapolation	Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population) or condition or product, thus reducing the need to generate additional information (e.g. types of studies, design modifications or number of patients required) to reach conclusions for the target population, or condition or medicinal product.
T6 Immunogenicity	The ability of a biotherapeutic product to provoke a humoral and/or cell-mediated immune response in animals or humans upon administration.
T7 Interchangeability	A designation that may be granted by medicine licensing agencies to two treatments that demonstrate the same efficacy and safety outcomes in clinical trials, and where alternating or switching products would not alter the expected clinical result.
T8 Off-label use	The use of a medicinal product for an unlicensed indication or a population, or in the manner of administration (route, dose or formulation) that is unlicensed and unintended by the manufacturer.

Term	Definition
T9 Oncology pharmacist	<p>A licensed or registered pharmacist with specialist training to provide cancer care, which usually includes offering evidence-based, patient-centred medicine therapy management, monitoring for potential adverse drug reactions and drug interactions, and providing medicinal and therapeutic information to healthcare professionals and patients to optimise usage of anti-cancer agents and supportive care. An oncology pharmacist also ensures aseptic preparation and provision of cancer chemotherapy, biotherapy and other supportive care medicines and directs appropriate administration of these agents.</p>
T10 Originator biotherapeutic product (also known as 'reference product')	<p>A biotherapeutic product, already approved by a regulatory body, against which a proposed biosimilar product is compared and evaluated to ensure that the biosimilar is highly similar and has no clinically meaningful differences. An originator biotherapeutic product is approved based on, among other things, a full complement of safety and effectiveness data.</p>
T11 Pharmacovigilance	<p>The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problems. The aim of pharmacovigilance is to enhance patient care and patient safety in relation to the use of medicines. This process should occur continuously throughout the life cycle of a medicine and for the duration it remains in the pharmaceutical market.</p>
T12 Product drift	<p>A change in the product or its characteristics that can occur over time or suddenly, for example, as a result of manufacturing changes. If a reference product undergoes a formulation or manufacturing change, the same tests used to establish a biosimilar are used to ensure that after the change, the reference product is similar to its original version. No additional clinical testing is required. This is known as product drift from the original reference product.</p>
T13 Switching	<p>An act by which an institution makes a collaborative and informed decision to exchange a reference product with a biosimilar or vice versa, with the common therapeutic intent, based on applicable local, regional and national policies.</p>

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