Edited by
Guy Regnard

Pharmacology

Fast Facts

Biosimilars

A Global Perspective

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HEALTHCARE

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Fast Facts for Healthcare Professionals

Pharmacology

Biosimilars: A Global Perspective

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Declaration of Independence

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List of abbreviations

ADA: anti-drug antibodies

ADCC: antibody-dependent cellular cytotoxicity

ADR: adverse drug reaction

API: active pharmaceutical ingredient

CDSCO: Central Drugs Standard Control Organization

CI: confidence interval

CKD: chronic kidney disease

CLL: chronic lymphocytic leukemia

CMC: chemistry, manufacturing and controls

DDD: daily defined doses

EMA: European Medicines Agency

EPAR: European public assessment report

EPO: erythropoietin

ESNO: European Specialist Nurses Organisation

FDA: Food and Drug Administration

G-CSF: granulocyte colony-stimulating factor

HLA: human leukocyte antigen

IBD: inflammatory bowel disease

ICB: intended copy biologic

INN: international non-proprietary drug name

IRR: infusion-related reactions

ISB: Indian similar biologic

IV: intravenous

KAMC-J: King Abdulaziz Medical City - Jeddah

KSA: The Kingdom of Saudi Arabia

LMIC: low- and middle-income country

MEA: Middle East and Africa

MENA: Middle East and North Africa

MNGHA: (Saudi) Ministry of National Guards Health Affairs

MOA: mechanisms of action

MRP: maximum retail price

NHS: National Health Service

ORR: overall rate of response

PAR: public assessment report

PD: pharmacodynamics

PK: pharmacokinetics

PRCA: pure red cell aplasia

PSUR: periodic safety update reporting

QSE: quality, safety and efficacy

rhEPO: recombinant human erythropoietin

SBOC: Brazilian Society of Clinical Oncology

SBP: similar biotherapeutic product

SC: subcutaneous

SDM: shared decision-making

SFDA: Saudi Food and Drug Authority

SPC: summary of product characteristics

STP: switch treatment period

TNF-α: tumor necrosis factor alfa

VEGF: vascular endothelial growth factor

WHO: World Health Organization

Introduction

Biologic medicines have revolutionized the treatment of many serious disorders. As biologic medicines are targeted specifically at disease processes, they typically offer a higher efficacy and lower toxicity than past generations of small-molecule synthetic chemical medicines. However, biologics come with a cost; for novel drug development, costs have risen over time, and biologic medicines are inherently more expensive to produce, thus restricting patient access. Furthermore, even when biologics have been available, reimbursement by national health systems has often been restricted to just a subset of the approved 'labeled' indications. Addressing this problem requires biologics to become more affordable and widely accessible without sacrificing their quality, safety and efficacy.

The first biologics reached patent expiry in 2006 in Europe, and lower-cost versions – biosimilar medicines – have been developed. The evidence, acquired over 15 years of clinical experience from 88 currently approved biosimilar drugs and over 2 billion patient-days' exposure in Europe, shows that approved biosimilars can be used as safely and effectively as originator biologics.[1] Biosimilar savings for Europe were estimated at US$ 4 billion in 2019, US$ 6.5 billion in 2021 and US$ 8.8 billion in 2022. In the USA, where legal issues delayed the approval of the first biosimilars 9 years later than in Europe, savings for 2021 were US$ 7 billion.

Biosimilars can potentially increase patient access to effective treatments; however, concerns persist about biosimilars, particularly in therapy areas where biosimilars are relatively recent additions to the formulary. The result has been uneven access, with only some health systems showing rapid biosimilar uptake that translates into financial benefits and increased patient access to treatment. Despite sharing a single medicines regulator, European uptake of biosimilar adalimumab has varied from 9% to 99%, with more than 90% for Norway, Poland and the UK, and 70–90% for Austria, Italy and Sweden.[2,3] In Latin America, in contrast, while recognizing the benefits of biosimilars, uptake has been slow except for Mexico, Argentina and Brazil, highlighting the disparity in accessing biosimilars.[4]

Lack of confidence in biosimilars has been reported to be highest in the world's middle-income countries, which could benefit the most

from more affordable biologics. Central to this has been the relative lack of effective medicines regulation and subsequent approval of follow-on biologics at regulatory standards lower than those used in Europe and the USA. For example, in 2021, only 1 of 54 African states had established a clear regulatory framework for biosimilar approval.[5] If regulatory standards are not the same, then follow-on biologics in those less regulated regions cannot assume that the real-world data of more than 2 billion successful patient-days' exposure to biosimilars in Europe applies to the medicines available in local pharmacies. This creates uncertainty that impacts confidence which in turn impacts patient access.

By way of an example, the International Diabetes Federation *Diabetes Atlas 2021* reports that Asia is the fastest-growing region for diabetes, yet the Joint Asia Diabetes Evaluation Program in 2019 found that even in the four highest biosimilar uptake nations, only 4.7% of patients were using biosimilar insulin (India, the Philippines, China and Vietnam).[6] The savings that middle-income nations could have made are significant. Biosimilar insulins in Brazil cost only 20 US cents for a defined daily dose, with the original reference brands being 86% more expensive at US$1.50 such that 100% biosimilar uptake would permit seven times as many people with diabetes to be treated for the same health budget.[7]

For this reason, *Fast Facts: Biosimilars* has taken a specifically global perspective, with expert contributors invited to represent a range of medical specialties, including endocrinology, hematology, oncology and immunology, and regions of the world. We address the following concerns, drawing on the most up-to-date information in this fast-moving area of medicine.

- Is the quality of the biosimilar medicine equivalent to that of the original drug?
- Is the biosimilar medicine safe?
- Which indications can the biosimilar medicine be used for?
- What are the realistic economic benefits?
- How do I switch a patient from a biologic to an equivalent biosimilar medicine?
- How do I select biologics in a region with regulatory uncertainty over biosimilars?
- How do I explain biosimilars to patients?

The answers are supported by a succinct explanation of the underlying science and regulatory principles, drawing on the significant experience accumulated within Europe and emerging global practice.

This concise, authoritative resource is intended to help clinicians and other healthcare decision-makers determine the value of biosimilars in clinical practice and aid discussions with patients.

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1 Definitions, development and economics

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We need biosimilars because we want access to biologics to treat a widening range of diseases, but we cannot afford their expense. Biosimilars deliver price discounts that can improve affordability and patient access by creating market competition once patents on the original reference medicine have expired. Readers will soon discover that terminology is a key issue in the field of biologics and biosimilars, with terms often used incorrectly, causing confusion (see page 24 for examples). Definitions of these terms are provided in the glossary below, Table 1.1.

TABLE 1.1

Glossary of terms

Term	Key definitions
Biological medicinal product (biologic)	• A medicinal product whose active substance is made by or derived from a living organism
Biosimilar medicinal product (biosimilar)	• Similar to a biologic that has already been authorized (the reference product). The active substance is highly similar to the one in the reference biologic, notwithstanding the natural variability inherent to all biologics (see page 24) • The name, appearance and packaging of the biosimilar may differ from those of the reference biologic, and the biosimilar may contain different inactive ingredients • The premise of a biosimilar is that there are no clinically meaningful differences between it and the reference medicine in terms of safety, quality and efficacy
Generic medicinal product	• In contrast to a biosimilar, a traditional generic medicine has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product • Appropriate bioavailability studies have demonstrated bioequivalence with the reference medicinal product

What are biologics?

Biologics are typically large macromolecules produced in living systems, such as bacterial, animal or human cell cultures, or are extracted from whole organisms. They range in size and structural complexity from simple proteins such as insulin and growth hormone to complex molecules such as coagulation factors and monoclonal antibodies, as shown in Figure 1.1. Many biologics, particularly monoclonal antibodies, are described as targeted therapies because they have been designed to interact with specific receptors on cells.

Chemical structures. Biologics are created in living systems and cannot be synthesized chemically. Most biologics are complex mixtures; while their primary and secondary structures are known, they are less easily characterized at the tertiary level. This stands in contrast to conventional 'small-molecule' drugs, which usually have a unique structure that can be fully characterized and are typically produced by inexpensive chemical synthesis that is straightforward to replicate. The complex nature of the biologics and their manufacturing processes means that identical copies of these molecules cannot be created.

Development. The term 'biologics' is now used to describe a growing range of therapies with a 'biological' origin, such as monoclonal antibodies, therapeutic proteins and peptides. These products are inherently more difficult and expensive to produce than

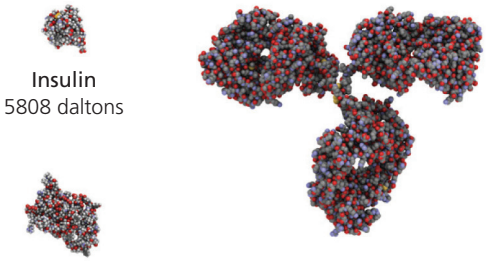

Figure 1.1 Examples of the varying complexity of biologics.[1]

past-generation synthetic medicines. Minor changes in the production process can significantly impact the final drug structure and its quality, safety, and efficacy. Furthermore, the rapid development of biotechnology means that production processes will likely be modified over time to produce biologics with a higher yield and greater purity than the original batches.

Drug developers frequently control their costs and manage capacity by outsourcing production to a 'contract manufacturer', often sited in low-wage regions,[2] and while manufacturing processes for biologics have several common features, many processes are kept unpublished and unreported at conferences or are protected by secondary patents and may only be revealed when biosimilars are developed. This creates a problem for medicine regulators as the production process of an originator 'reference biologic' will change over time and because a second manufacturer is unlikely to use the same biotechnology process. This explains why biologics may be highly similar over time but can rarely be characterized as 'identical'.[3]

Higher specificity. Biologic medicines have been described as the medicines of the future because of their ability to transform many once hard-to-treat diseases. They achieve this through a higher specificity, higher activity and lower toxicity than the past generations of typically synthetic chemical medicines that preceded them.[4] Higher specificity from biologics comes from their activity that can be 'targeted' to interact with receptors or signaling molecules, or are, themselves, signaling or regulatory molecules that are central to the disease process. Examples would include trastuzumab – targeted to the HER2 receptor over-expressed on aggressive subsets of breast cancer; infliximab – which binds the tumor necrosis factor signaling molecule that drives many inflammatory disorders such as rheumatoid disease and ulcerative colitis; or insulin glargine – an analog of human insulin modified to deliver a prolonged action – that acts as a regulatory hormone of glycemic control in diabetes.

What are small-molecule drugs?

In comparison, small-molecule drugs make up most drugs we use by volume. They usually have a well-defined chemical structure and a known mechanism of action. Their efficacy can be modified by

generating multiple chemical variants in so-called 'drug libraries' that can be assessed in vitro by interacting with fully characterized drug targets, a process known as 'rational drug design'. They can usually be made synthetically with high purities and yields using well-defined, standard manufacturing processes that are straightforward to replicate.

Limitations of small-molecule drugs. Small-molecule medicines are limited to diseases with a defined chemical binding site. However, not all disease processes are clearly understood or deliver a classic 'druggable' binding site for developers to target. Without knowledge of the structure and function of the target, it becomes impossible to use rational drug design, and instead, the process relies on trial and error. In contrast, the much greater size of a typical biologic medicine enables them to establish larger contact areas with less-defined targets such as protein molecules and DNA.

This produces stronger binding than could be achieved by small molecules with the potential for greater specificity and efficacy that can translate to medicines with higher potency with less toxicity.[5]

Why do we need biosimilars?

Costs. The transition from small-molecule drugs to biologics may have provided advances in treating many conditions, but it has markedly increased drug expenditure. For example, 8 weeks of standard chemotherapy for advanced colorectal cancer cost US$ 63 in the small-molecule era but US$ 30 790 using biologics, representing an almost 500-fold increase in drug costs – although this has been accompanied by improved outcomes. Manufacturers justify the high prices of biologics based on the investment in discovery, development and production. Between 2022 and 2026 the majority of new drugs launched worldwide will be biologics and US$ 196 billion will be needed to pay for them. This is at a time when new investment is in short supply as the economic shock from the COVID-19 pandemic has increased government and personal borrowing worldwide.[6]

Economic comparison with generics. The economic impact of biosimilars differs slightly from that of generics. While introducing biosimilars decreases price and increases access, this effect is often less than that observed for generics. Furthermore, the competitive

response to price reductions by reference biologics is often heterogeneous. In the small-molecule market, the introduction of generics does not change the price of the reference drug, leading to a loss of 70–90% in sales in the first year.

In contrast, two patterns emerge with the introduction of biosimilars, both resulting in a decrease in the reference biologic price in response to competition.[7] The first response is a decrease in the price of the reference biologic as biosimilars are introduced to the market, enabling the reference biologic to retain a large market share. In the second response, price reductions in the reference biologic are in response to large shifts in volume away from the reference biologic. The first response can prevent biosimilars from establishing market share, enabling the reference biologic to possibly exercise market power in the long term.[7]

Cost versus access. While discussing costs may make some clinicians uncomfortable, it is a reality of modern medicine. Given aging populations and the rising prevalence of chronic conditions and cancers for which biologics are used, biologics represent a major demand on healthcare budgets that are already under pressure, and rationing measures are inevitably applied. However, just as the introduction of generic versions following the patent expiry of small-molecule drugs drove down prices, biosimilars can be expected to lower the costs of biologics. The substantial savings realized can improve patient access by allowing more patients to be treated from the same budget. Thus, biosimilars will enable stakeholders – including payers, clinicians, and patients – to benefit from a greater choice of treatment options, and more patients will have access to these treatments.

In the USA, biosimilar use is expected to result in savings of US$ 38.4 billion from 2021 to 2025, representing 5.9% of the projected biologic spending in the USA for that period. This estimated saving jumps to US$ 124.5 billion in a scenario where there is aggressive biosimilar uptake and competition. The main contributor to these savings is the downward pressure on reference biologic prices rather than the affordability of biosimilars (Figure 1.2).[8]

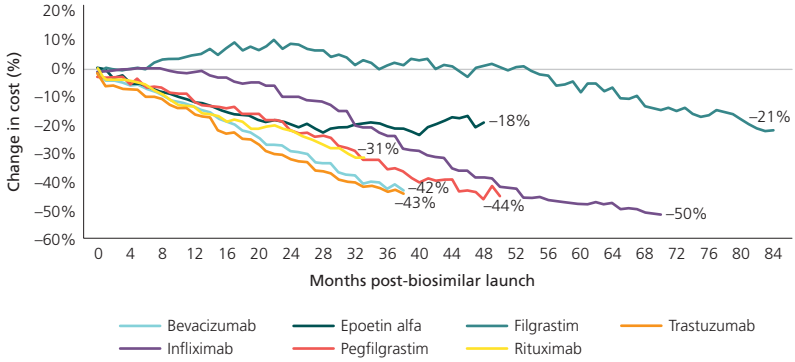

Figure 1.2 Change in reference biologic prices relative to 1 month before biosimilar launch.[9]
Source IQVIA.

For each biosimilar that enters the market, the weighted average market price of the reference biologic has been estimated to fall between 5.4% and 7%.[7] This highlights the importance of ensuring biosimilars enter the market and compete with the biologic.

In Europe, similar savings have been reported, with biosimilars only representing €9 billion annually, but their competition has had a downward pressure on reference biologics, providing further annual savings of €4.47 billion. In 2022, 18 molecules had an average of 3.8 biosimilar competitors in Europe.[10,11]

Approximately 80% of monoclonal antibody sales are in Western countries; however, 85% of the global population resides in low- and middle-income countries (LMICs); therefore, an opportunity exists for biosimilars to expand access across these countries.[12]

The Middle East and Africa (MEA) represents an emerging pharmaceutical market, with biosimilars in the Middle East and North Africa representing US$ 442.5 million in 2020 and expected to grow to US$ 626.7 million by 2027. The uptake of biosimilars in the MEA has already increased from 1.0% in 2018 to 4.3% in 2022.[13]

Rational prescribing. In creating national policies, it should be noted that prescribing of biosimilars is entirely in keeping with the concept

of 'rational prescribing' defined by the WHO, which includes a cost imperative added in 2011:

> Medicine use is rational (appropriate, proper, correct) when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community.[14]

In 2020, the WHO's updated guidelines on country pharmaceutical pricing policies strongly recommended that countries promote quality-assured biosimilars as part of a strategy designed to overcome unaffordable pharmaceutical prices. The guidelines recommend enabling early market entry of biosimilars, using multiple policies to generate greater market competition, and maximizing biosimilar uptake and public confidence.[15] Furthermore, the European Commission has proposed reforms to EU pharmaceutical legislation that include increasing competition through faster biosimilar market entry, reducing biosimilar prices and promoting patient affordability and sustainability of healthcare systems. These reforms aim to encourage timely and equitable patient access to medicines.[16]

Adoption of biosimilars requires education of clinicians and other healthcare professionals about the benefits and safety of biosimilars and addressing some of the concerns that persist – even though there have been no efficacy or safety concerns during the first 15 years of biosimilar use, corresponding to more than 2 billion patient-days' exposure to European-approved biosimilars.

Key points – definitions, development and economics

- Biologics are medicines created in living systems, such as bacterial, animal or human cell cultures, or are extracted from whole organisms.
- Biologics are typically large complex molecules and are described as medicines of the future because of their higher therapeutic index than past generations of small-molecule synthetic drugs.
- Biologics have provided major advances in treating many chronic conditions and cancers but are a major burden on healthcare budgets. Biosimilars provide a valid lower-cost replacement to original-brand biologics.
- Biosimilars will enable payers, clinicians, and patients to benefit from a greater choice of biologics and, through price reductions, more patients will have access to these treatments.
- The prescribing of biosimilars is in keeping with the concept of rational prescribing, which includes a cost imperative.

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2 Biosimilars vs reference biologics: variability and comparability

HEALTHCARE

Biosimilar medicines

Biosimilar medicines are follow-on versions of an original 'reference' biologic medicine that has lost patent protection and has been developed by a second manufacturer. In the early years of regulation, many different terms were used for follow-on brand biologics. In Canada, they were referred to as 'subsequent entry biologics', while the US regulator preferred 'follow-on biologic', and the WHO used 'similar biotherapeutic products' for its WHA67.21 guidelines. Only after the successful launch of the first-generation follow-on biologics in Europe did 'biosimilar' become adopted by other agencies, and it took until April 2022 before the WHO terminology showed a corresponding shift to biosimilar rather than 'similar biotherapeutic product'. This terminology will matter later, as there are now two general meanings for that term. The first is a strict regulatory term for follow-on biologics developed and regulated to meet the European, US and WHO guideline standards. The second has become a marketing term for any follow-on biologic developed to any regulatory standard. This distinction matters and will be the focus of later sections of this book. For clarity, we use the term biosimilar only in its strict regulatory meaning.

Variability in biologics. As its name suggests, a biosimilar is highly similar to the reference biologic product but is not identical. The primary and secondary amino acid structure, dosing, and route of administration are the same; differences in formulation, presentation, and administration device are permitted, provided these differences do not affect safety or effectiveness. As with all biologic medicines, the challenge for manufacturers and regulators is to ensure that copies of biologics are close enough in structure and function to the reference product to have no clinically meaningful differences in practical use.

There is intrinsic variability in the biologics themselves – an important point relevant to discussing biologics and biosimilars that is often overlooked. This variability has two primary sources.

Microheterogeneity. Molecules made in living systems have inherent variability, even between batches of the same product, known as microheterogeneity. Thus, over time, a reference drug can

never be considered a generic copy of its version at launch, as illustrated in Figure 2.1.[1] This inherent variation is known as 'product drift' (Figure 2.2).[2]

Manufacturing. The manufacturing process can impact aspects of the structure of a biological drug; a copied biologic can, therefore, never be entirely identical to the original reference product. Thus, the active substance of a biosimilar and its reference biologic is almost the same biological substance, but there may be minor differences due to their complex nature and production methods. Like the reference (originator) biologic, the biosimilar has a degree of natural variability. When a biosimilar is approved, this variability, and any differences between the biosimilar and the reference biologic, will have been shown not to affect safety or effectiveness.

In addition, manufacturing processes change frequently over the life of a biologic, adding to the potential for variability. Reasons for manufacturers making intentional process changes include improvements, scale-ups or site transfers.[3] A 2022 study of European

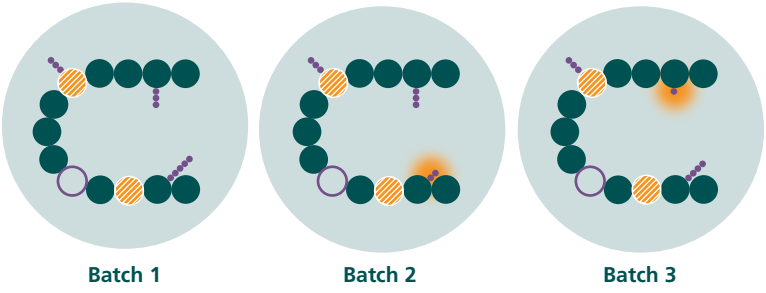

Figure 2.1 Microheterogeneity of drug structure: variability between different batches of a biologic. Consecutive batches of the same biologic may show a small degree of variability (yellow shadow) within the accepted ranges, for example in glycosylation (sugar molecules attached to the protein, shown by small blue circles). The amino acid sequence (large circles) and biological activity of the protein remain the same in all batches, even when there are minor differences in the sugar chains. Adapted from European Medicines Agency, 2024.[1]

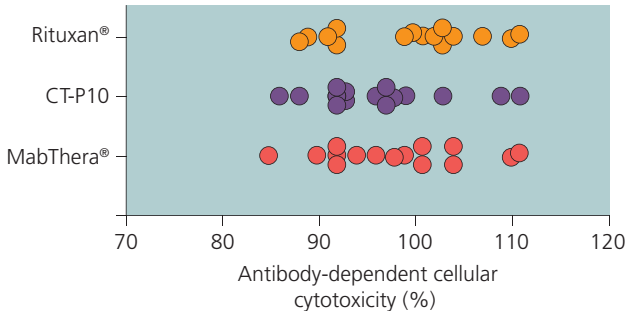

Figure 2.2 Microheterogeneity of function between different batches of a biologic medicine. This scatter plot compares the antibody-dependent cellular cytotoxicity (ADCC) of different batches of rituximab, measured as a % ADCC using antibody at a concentration of 0.035 µg/mL. Three different brands are compared, originator rituximab brands Rituxan® (USA) and MabThera® (European) and a proposed biosimilar, CT-P10. In this example taken from an Food and Drug Administration (FDA) assessment report, despite variation, the 90% confidence intervals (CIs) of the mean difference between CT-P10 and Rituxan® and between MabThera® and Rituxan® were within the equivalence margin.[2]

Medicines Agency (EMA)-approved reference biologics and biosimilars of tumor necrosis factor alfa (TNF-α) inhibitors up to May 2021 identified 801 post-approval manufacturing changes (Figure 2.3). Of these changes, 88.1% were classified as low and medium risk, while 11.9% were considered high risk. The average incidence rates between reference biologics and biosimilars were comparable at 7.0 manufacturing changes per year and 0.8 high-risk manufacturing changes per year. The authors concluded that data indicated no reason for manufacturing changes to result in clinical differences between reference biologics and biosimilars (Figure 2.4).[4] Changes in manufacturing risk the introduction of more significant variation in the tertiary structure of a biologic, known as 'step changes' (Figure 2.5).

Comparability of the drug before and after a step change must be demonstrated to ensure that safety and efficacy have not changed. This comparability is usually assessed using only analytical tests, and new regulatory trials are rarely required. One example is a step change

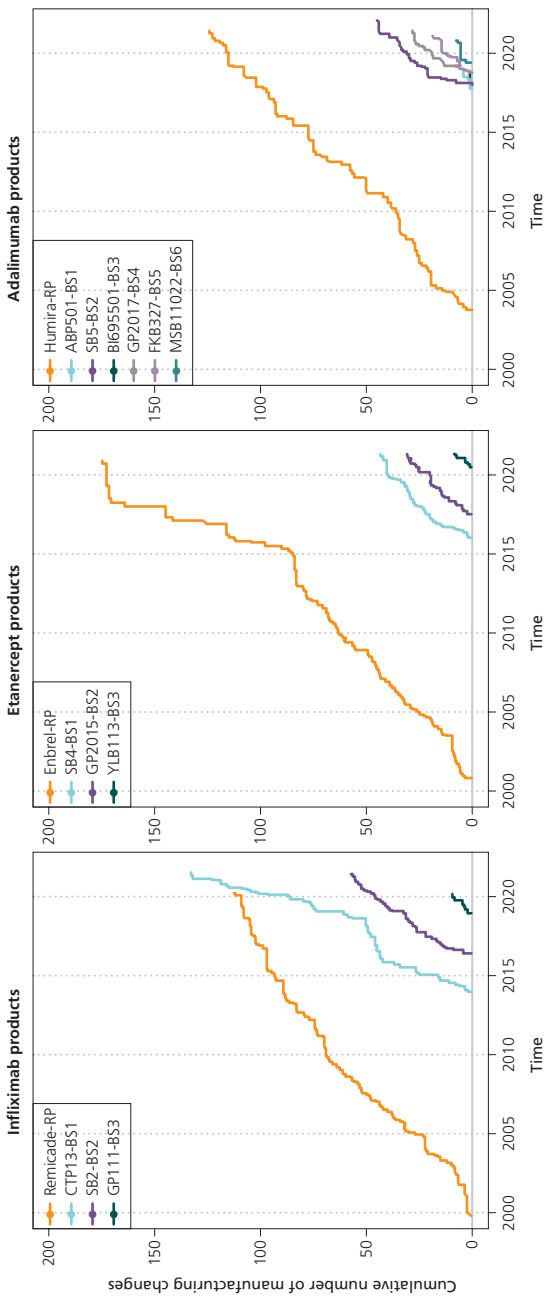

Figure 2.3 Cumulative number of post-approval manufacturing changes of EMA-approved reference biologics and biosimilars of TNF-α inhibitors up to May 2021.[4] Adapted from Alsamil et al. 2024.

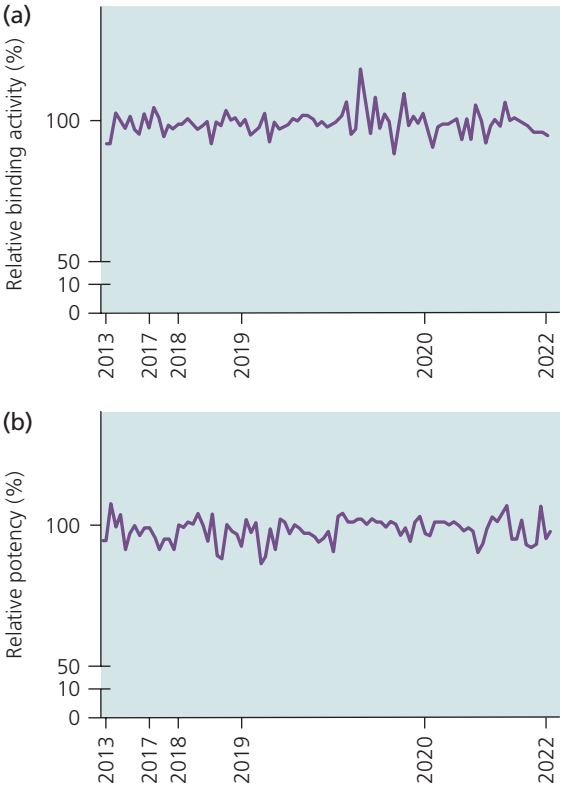

Figure 2.4 The consistency of biological activity for the adalimumab biosimilar, SB5, from 2013 to 2022, during which manufacturing changes included site transfers and formulation changes. (a) TNF-α binding activity ranged from 86 to 108% (mean 99%, SD 4%), and (b) TNF-α neutralizing potency ranged from 88 to 119% (mean 98%, SD 4%). All 93 batches were produced within the acceptance criteria.[3] Adapted from Lee et al. 2023.

resulting from a new process in manufacturing darbepoetin-alfa, which required confirmation through additional phase I, II, and III studies. For this reason, manufacturing changes are monitored closely under the 2014 International Council for Harmonisation Q5E.[5]

Bioidenticals and 'intended copy' biologics. These terms are mentioned here because they occur in the context of biologics and biosimilars and are potentially confusing.

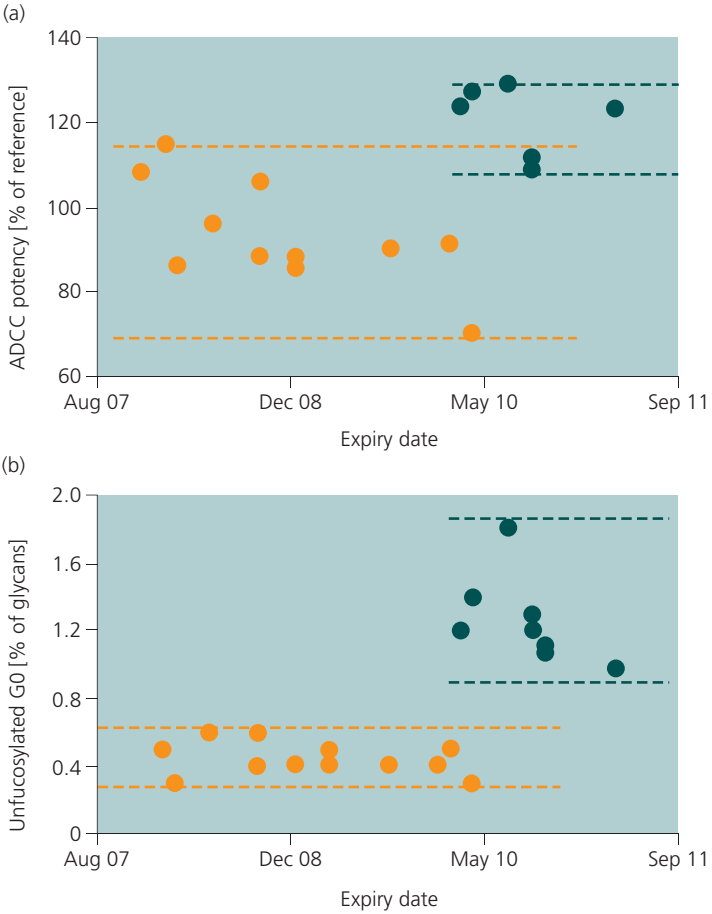

Figure 2.5 The concepts of 'drift' and 'step changes' as sources of variation in critical attributes of a biologic over time. (a) Versions of a reference biologic with expiry dates up to May 2010 show 'drift' in the critical attribute of antibody-dependent cell-mediated cytotoxicity (ADCC) until biopotency is reported at less than 80% of the initial reference activity, threatening to compromise clinical outcomes. A 'step' change in activity is then seen in batches dated after May 2010. Subsequent examination shows that this change resulted from a manufacturing 'step change' that altered the fucose levels of the drug (b). Thus, a 'new version' of the drug was created with different critical attributes from previous batches. Changes in fucosylation of the crystallizable fragment (Fc) region of a monoclonal antibody are a potent way to alter its activity.[6] Adapted from Schiestl et al. 2011.[7]

TABLE 2.1

Examples of bioidenticals: products that are the same but with different brand names

Drug	Bioidentical brand names	Market authorization holder
Infliximab	Inflectra	Hospira UK
	Remsima	Celltrion Healthcare Hungary
Epoetin alfa	Abseamed	Medice Arzneimittel Pütter
	Binocrit	Sandoz
	Epoetin alfa Hexal	Hexal Biotech
Epoetin zeta	Retacrit	Hospira UK
	Silapo	Stada Arzneimittel
Rituximab	Blitzima	Celltrion Healthcare Hungary
	Ritemvia	
	Rituzena (previously Tuxella)	
Trastuzumab	Truxima	
	Herceptin	Roche Products Limited
	Herclon	Emcure Pharmaceuticals India & Roche

Bioidenticals are products that are the same but have different brand names (as can also occur with small-molecule drugs); some examples of bioidenticals are provided in Table 2.1. These can arise when a product is co-developed but marketed by different manufacturers in different countries under different brand names. Different brand names may also be used for a biosimilar of a reference product that still has patent protection for some indications, particularly in Europe, where the EMA approves medicines for use in more than 30 countries.

Intended copy biologics (ICBs) have arisen in markets with less stringent regulatory pathways, as a way to deliver affordable medicines. The definition of an ICB is "a biotherapeutic product developed on its own and not directly compared and analyzed using a licensed reference biotherapeutic product as a comparator. It may or may not have been compared clinically".[8] While clinically active, such medication may not be close enough to the originator molecule to be judged biosimilar in analytical or clinical testing. Without either a 'biosimilarity exercise' or the security of a Phase III trial in each indication (for extrapolation cannot be approved in the absence of biosimilarity or a pivotal clinical trial), the safety and efficacy of such medicines cannot be predicted.[9]

A survey of 20 countries conducted in 2020 by the WHO in collaboration with national regulatory agencies identified several countries where ICBs were still approved: Brazil, China, Egypt, Jordan, Ukraine, and Zambia. ICBs were mainly produced for human insulin (67), while China had the most approved ICBs, at 98. As national regulatory pathways evolve and align with WHO standards, previously approved ICBs currently on the market may no longer meet regulatory expectations and be deemed inappropriate for clinical use. These products would need to be re-evaluated in such instances, and the WHO has developed guidelines for assessing such products, with several countries having already taken action to review such products in their markets.[8]

While ICBs are unlikely to be encountered in clinical practice in the EU and USA, it should be borne in mind that such products have been misleadingly identified as biosimilars. Examples of clinical problems that have arisen following the use of such products are described on pages 82–5). In the press, these products were referred to as biosimilars; incidents such as these may fuel concerns with true biosimilars where such concerns are unfounded. Note that ICBs have also been referred to as 'non-innovative products', 'non-comparable biotherapeutic products', 'biomimics', 'bio-generics', and 'bio-questionables'.

Key points – biosimilars vs reference biologics: variability and comparability

- Biologics are typically proteins, ranging in size from simple proteins to large, complex monoclonal antibodies. They are created in living systems.
- Inherent variability exists for all biologics and creates batch-to-batch variability for all products.
- Biosimilars are *highly similar*, but not identical, to their reference (originator) biologic. Furthermore, biologics themselves show inherent variation between batches (microheterogeneity), such that no batch is identical to previous batches.
- The slight differences between batches of biologics, or between biologics and biosimilars, are authorized and not expected to have any meaningful effect on clinical use.
- Changes to manufacturing processes can introduce significant changes to the tertiary structure of a biologic; analytical tests (and, exceptionally, new clinical trials) are required to assure that safety and efficacy have not changed.
- Bioidenticals are products that are the same but have different brand names.
- ICBs are not biosimilars but products developed under less stringent regulatory pathways without being directly compared and analyzed using a licensed reference biotherapeutic product as a comparator.

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Pharmacology

3 How are biosimilars approved in Europe and the USA?

HEALTHCARE

The central role of medicines regulators is to ensure the quality, safety, and efficacy (QSE) of medicines. The critical step to approval for novel medicines is the data generated by the 'pivotal clinical trial'. For most medicines, this involves a definitive Phase III randomized trial comparing the current standard of care and the novel therapy, already studied in Phase I and II trials to determine the optimal dose, pharmacokinetics (PK) and dynamics, and identify the likely side-effect profile. For follow-on medicines, generics and biosimilars, the regulator needs to demonstrate the 'sameness' of the QSE of the new brand compared with the original 'reference brand'.

For generics, which are copies of small-molecule synthetic medicines, the regulation is typically straightforward as the active pharmaceutical ingredient (API) needs to be identical while the formulation has to be bioequivalent to the innovator drug to ensure the same biological effect with similar safety and efficacy.

In contrast, biologics have no clearly defined API structure (Table 3.1). The primary amino acid sequence of a protein drug may be identical, but there are complexities of structure as well as protein modifications such as glycosylation. Furthermore, potency, PK and immunogenicity may be altered significantly by post-translational changes that may vary with production conditions. This explains the inherent variability of biologics, as described in the last chapter, and why a generic approach to biosimilar regulation is scientifically unacceptable.

Biosimilar development. A 2022 McKinsey and Company analysis estimates that biosimilar development costs between US$ 100 million and US$ 300 million, with a 6–9-year timeline from analytical characterization to approval.[1] In contrast, according to Pfizer, a generic costs US$ 1–2 million and takes approximately 2 years to develop.

Target mapping. Biosimilar developers need to map the limits of variability in structure and function of the reference biologic over time by purchasing many different batches (often from various world regions) to define those limits. This is called 'target mapping'. To achieve this for a complex structure such as a monoclonal antibody requires state-of-the-art analytical chemistry and sensitive measures of drug potency. In addition, regulators require that no single test is used for each critical attribute of the reference brand. Instead, developers

TABLE 3.1

Comparison of the development and characteristics of generic and biosimilar medicines

	Generic medicine	Biosimilar medicine
Source	Usually chemical synthesis	Biological
Type of molecule	Small molecule	Larger, structurally complex molecule
Characterization	Easily characterized	Multiple technologies required for characterization
Degree of similarity	Generally possible to obtain exactly the same molecule	High degree of similarity reflecting unique biomanufacturing methods and natural biological variability
Data requirements on pharmaceutical quality	Full	Full, plus quality studies comparing the structure and biological activity of the biosimilar vs the reference medicine
Basis of development	Demonstration of *bioequivalence* (i.e. that the generic and reference medicines release the active substance at the same rate and to the same extent under similar conditions)	Demonstration of *biosimilarity* through comparability studies: comprehensive head-to-head comparison of the biosimilar and reference medicine to show high similarity in chemical structure, biological function, efficacy, safety and immunogenicity
Clinical data requirements	Mainly, pharmacokinetic bioequivalence studies	Comparative pharmacokinetic-pharmacodynamic studies Safety and efficacy data may be required for more complex biologics

CONTINUED

TABLE 3.1 CONTINUED

Comparison of the development and characteristics of generic and biosimilar medicines

	Generic medicine	Biosimilar medicine
Indications	All indications approved for the reference medicine can be granted based on a demonstration of bioequivalence without further clinical data	Efficacy and safety have to be justified in each indication, but confirmatory trials are usually not needed in every indication approved for the reference medicine – after demonstration of biosimilarity, extrapolation of data to other indications is possible if the scientific evidence available addresses all specific aspects of these indications

Adapted from European Medicines Agency 2019.[2]

need to use multiple 'orthogonal' overlapping tests, with often a hundred in vitro analytical tests required to define the reference biologic variability before any animal or human studies can begin. Even then, there may be uncertainties about a biosimilar QSE.

Original reference medicines are protected at launch by patent law and laws on data exclusivity. This delays biosimilar developers from using the originator test data submitted for marketing approval when seeking such approval for their product. Data exclusivity does not prevent biosimilar companies from generating their own efficacy data; however, these costs are prohibitive.[3]

The biosimilar maker must often try to copy a moving target once the exclusivity period ends. Not only can the reference product show drift and step changes over time, but the manufacturers of original reference drugs are incentivized to prolong patent protection to protect their monopoly. One strategy is secondary patenting or 'evergreening' by introducing minor changes to a product, which are then patented, thereby extending the exclusivity period. Blockbuster drugs can have patent portfolios that run into the hundreds.[4]

Biosimilars have a development advantage in that they are built on the large body of evidence created by the originator medicine and available at the time of the biosimilar's development. This totality of experience available with the original reference product can highlight issues such as immunogenicity or multiple potential mechanisms of action (MOA) that will be critical in developing follow-on products. Manufacturers and regulators define quality according to critical 'quality attributes': chemical, physical, and biological properties within agreed tolerances. Advances in analytical technology have permitted detailed characterization of the active ingredients in biologics. Importantly, for biosimilarity with a reference protein product, it is necessary to demonstrate that the amino acid sequence (primary structure) and higher order structure are the same.[2]

Developmental corridor. The upper and lower limits of the tolerance are referred to as the 'developmental corridor' (Figure 3.1);[5] quality control monitoring of production batches by manufacturers ensures that the product reaching the patient is within the developmental corridor, such that a predictable effect can be expected. Once biosimilarity at a molecular level is established, it is confirmed through limited clinical trials.

Batches of biologics vary over time, and this is true for both the originator and biosimilar drug. Clinical studies of an originator drug to support different indications will likely have been conducted with different batches. Indeed, it is possible that a biosimilar batch could more closely share critical attributes of that (originator) batch than the current batch. A change in the production process of a biological drug (originator or biosimilar) could affect outcomes. For this reason, manufacturing changes are regulated to ensure that new batches of products meet the defined critical attributes.[6,7]

The regulation of biosimilar production is based on the procedures developed to address changes to manufacturing originator biologics. Biologic and biosimilar drug developers can determine the natural variation in the structure and biopotency of the reference drug from sequential batches of the drug. Variation in these attributes over time defines the limits of acceptable analytical differences that a regulator accepts between a reference drug and its biosimilar, establishing the developmental corridor for a biosimilar.[8]

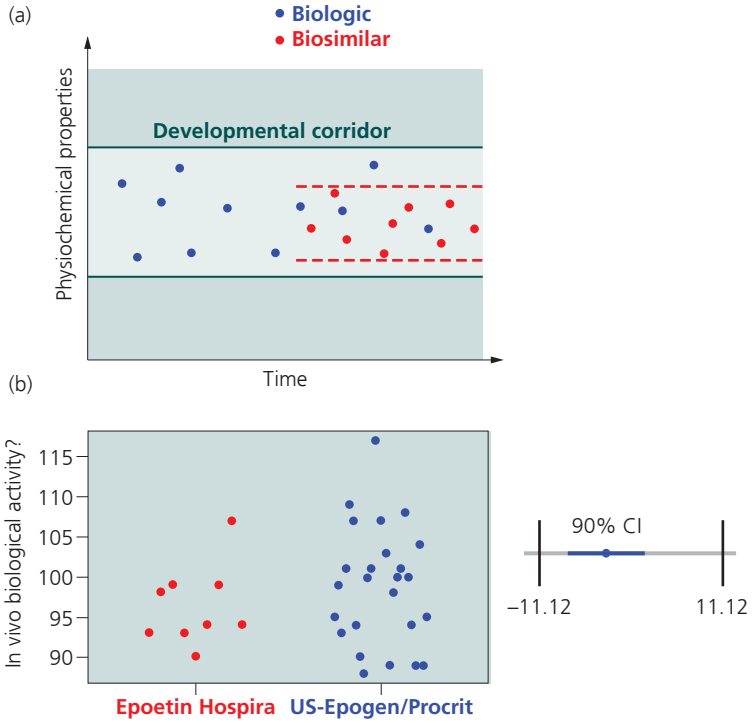

Figure 3.1 The developmental corridor: (a) the concept and (b) equivalence data for epoetin. Each point on the graphs represents one batch of biologic or biosimilar. (b) Scatter plot of drug product lot values for the in vivo activity of Epoetin Hospira (the biosimilar) and US-licensed Epogen/Procrit (the reference biologic); the equivalence test plot on the right shows that the 90% confidence interval (CI) for mean difference (the blue margin) is well within the equivalence margin (shown by the black vertical lines).[5]
Source: FDA.

In some circumstances, a biosimilar that has a notable difference in a critical attribute from the reference product may be permitted by regulators, as in the example of epoetin alfa: a biosimilar version is available that has a relatively high level of phosphorylated mannose-type structures (compared with the reference compound).[9] The European Medicines Agency (EMA) accepted this difference on the basis that these structures are considered to be common glycoforms

of recombinant erythropoietins and that their presence has been described in the literature for other recombinant cytokines and a large variety of non-lysosomal proteins from human plasma. The level observed did not affect the efficacy or safety.[10]

Once a biosimilar target has been defined and the limits of the developmental corridor identified, a biosimilar maker will go through many rounds of host cell cloning, cell growth, and product harvesting under different production conditions to develop the optimal product. Crucially, the biosimilar developer cannot access information such as the innovator manufacturer's host cell line, cell culture conditions, purification procedures, and fill and finish processes where the final biologic is put into vials or pre-filled syringes before sale. Further, the biosimilar manufacturer cannot access information about the innovator manufacturer's product development history, such as manufacturing process changes. Readers should note that much of that information will have been shared with the relevant medicines' regulator, the same agency that will be assessing the biosimilar.

Once a reliable host cell clone and production process has been identified, the developer may have *made a biosimilar,* but the next step is to *prove biosimilarity* to the reference biologic sufficient to ensure that no clinically significant difference can arise.

Stepwise development and regulation. For regulators in Europe and the USA, and the WHO, the regulatory assessment process is described as 'stepwise', illustrated in Figure 3.2. At each step, the critical attribute of the drug must have been shown to be comparable to the reference biologic, such that there is no significant residual uncertainty before development and assessment proceed to the next step. Reports from European and US regulators indicate that developers and regulators are in frequent conversations as development proceeds. There are indications that some development steps have been repeated or modified due to this process. The result is a degree of shared responsibility for the development pathways of many biosimilars and explains why so few are rejected by regulators at a late stage of development.

A biosimilar is approved at the final assessment stage based on the 'totality' of data gained across multiple comparability tests recorded in a typical biosimilar assessment report. Crucially, not all tests have to be comparable if there is good evidence that any variation will not

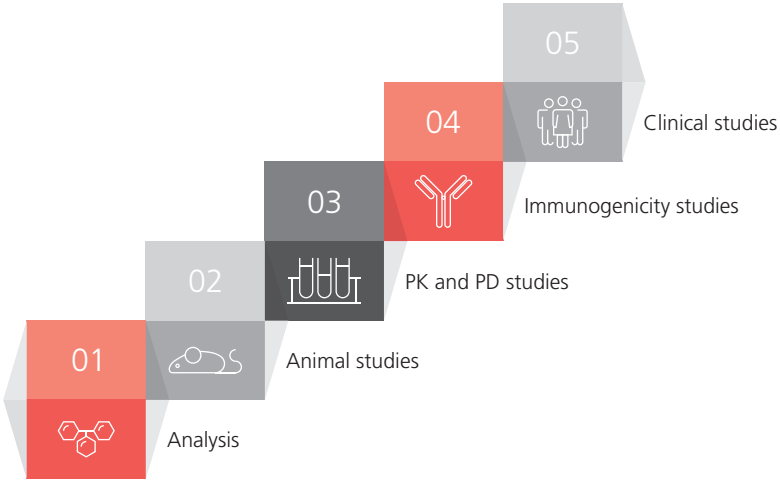

Figure 3.2 The 'stepwise' assessment of a proposed biosimilar, using the methodology of the European and US regulators and as adopted by the WHO. At each step, the critical attributes of the biosimilar must have been shown to be comparable to the reference biologic, such that there is no significant residual uncertainty before development and assessment proceed to the next step. The final decision for regulatory approval is made based on the 'totality' of the data on comparability gained over all the steps. PD, pharmacodynamics; PK, pharmacokinetics. Adapted from Cornes 2017.[11]

lead to a significant clinical difference. This has led many to state that biosimilars are 'similar but not identical' compared with the 'identicality' principle of the more familiar small-molecule generics.

The clinical trial stage of development contains requirements to show comparable PK, pharmacodynamics (PD), immunogenicity and safety. This is because, with biologic medicines, these endpoints cannot be reliably predicted from analytical, cell, or animal studies. Although many confirmatory head-to-head trials report clinical endpoints, regulators explain that these may be the least sensitive of the many comparability tests for detecting a difference.

There is no doubt that biosimilars would have been treated like generic products if it was possible to define them as chemically equivalent. This explains why, for regulators, analytical assessment gives the most confidence in comparability. This seemingly low

priority placed on clinical trials may cause concerns to prescribers, as described by WHO regulators Kang & Knezevic in 2018.[12]

> "Prescribers, such as physicians and clinicians, tend to judge the safety and efficacy of medicines using clinical trial data."

> "Usually, analytical assessments are more sensitive for detecting differences between, or changes in, products than the endpoints used in clinical trials."

The priority of clinical studies for novel drug approval and analytical studies for biosimilars has led to the regulatory pathway being described as an opposite triangle.[5] However, both paths have a strong similarity in their content, and the emphasis placed by the triangle descriptions may be misleading (Figure 3.3).[13] Indeed, for many biosimilars, the comparative efficacy trials conducted to obtain Food and Drug Administration (FDA) approval have been larger, longer, and more costly than clinical trials required for originator products.[14]

Concerns about immunogenicity. Immunogenicity is a potential safety concern with any biological agent, and even slight changes in structural properties or innate immune response modulating impurities could, in theory, trigger an adverse immune reaction.[15] Product drift over time and evolution through manufacturing changes may produce

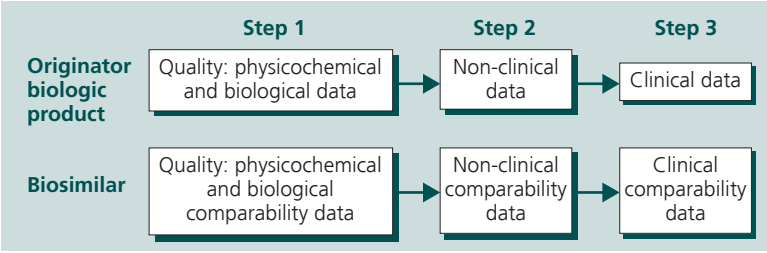

Figure 3.3 Comparison of the approval processes for a biosimilar and its reference product according to the EMA biosimilar pathway. Adapted from Khraishi et al., 2016.[13]

structural differences in a reference biologic, meaning that no biologic can ever be considered truly identical to itself over time.

Immunogenicity cannot yet be predicted from analytical or animal studies with sufficient accuracy for biologic medicines. For this reason, clinical studies in humans remain a requirement for biosimilar medicines (though not routinely required for a biologic drug undergoing a manufacturing change or small-molecule generics). Regulators are concerned with identifying differences in toxic potential, such as acute anaphylaxis or decrease in drug efficacy through the development of neutralizing anti-drug antibodies (ADA) that increase the clearance of the drug.[16] Immunogenicity is monitored both pre- and post-marketing.[2] Biosimilars do not have to show that they have no immunogenicity – just that the levels are similar to those of the originator.

Anxieties about immunogenicity appear to be generally unfounded, and both the comparative clinical trials and post-marketing studies indicate that European-approved biosimilars have not been associated with any increase in the incidence of such adverse events. In contrast, documented immunogenicity differences with clinical impact have been reported for originator medicines undergoing manufacturing changes and with intended copy biologic drugs from less regulated medical regions of the world. Figure 3.4 illustrates immunogenicity data for biosimilar adalimumab and the reference brand, Humira™.[17]

Pharmacokinetic studies. These are frequently the first-in-human studies of a biosimilar and are important because post-translational modifications of biologics can lead to very different distributions of the drug in humans.

Figure 3.5 demonstrates the similar PK profile of MB02, a biosimilar of the humanized monoclonal antibody bevacizumab (Avastin®) that inhibits angiogenesis by binding to vascular endothelial growth factor (VEGF), thereby preventing its interaction with VEGF receptors found on endothelial cells. Bevacizumab was initially approved for the treatment of metastatic colorectal cancer but has since been expanded to incorporate a wide range of oncology indications.[18]

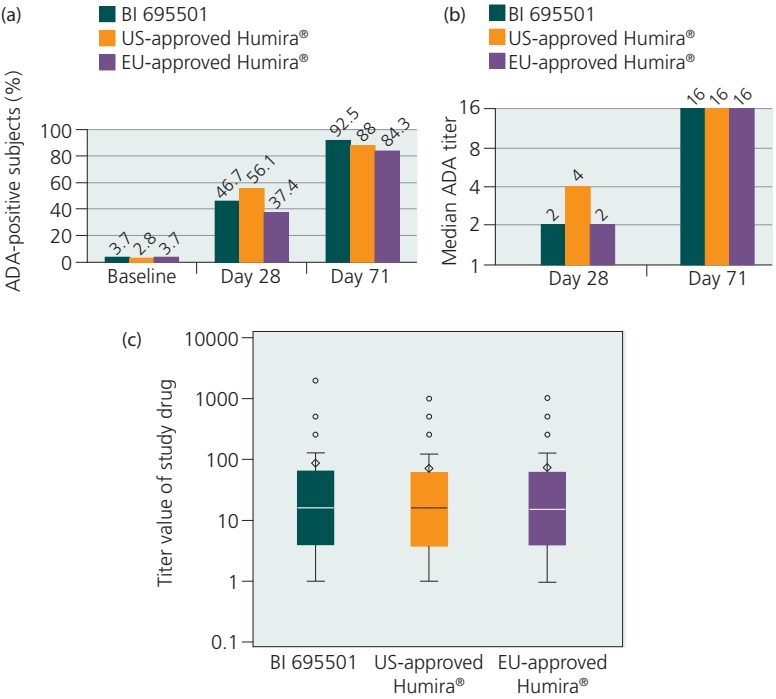

Figure 3.4 Comparable immunogenicity of biosimilar adalimumab (BI 695501) and the originator biologic Humira. The graphs demonstrate the similar immunogenicity of the biosimilar and originator biologic in healthy subjects after a single dose of study drug. (a) Frequency of ADA-positive responses; (b) median ADA titer, and (c) end-of-study titers for healthy subjects with ADA-positive responses. Median values are depicted by a line within the 25% and 75% percentile boxes; a diamond shows the arithmetic mean; individual points are outliers; the vertical lines out of the box plot represent minimum and maximum values or 1.5× interquartile range. Reproduced with permission from Wynne et al., 2016.[17]

Clinical confirmatory studies. Prescribers are often familiar with the design and interpretation of 'pivotal' Phase III clinical trials for novel medicines. The endpoint is usually a clinical outcome, and the aim is to show the statistical superiority of the novel treatment compared with the current standard of care and record toxicity data to decide if the balance of risks and benefits supports drug approval. The

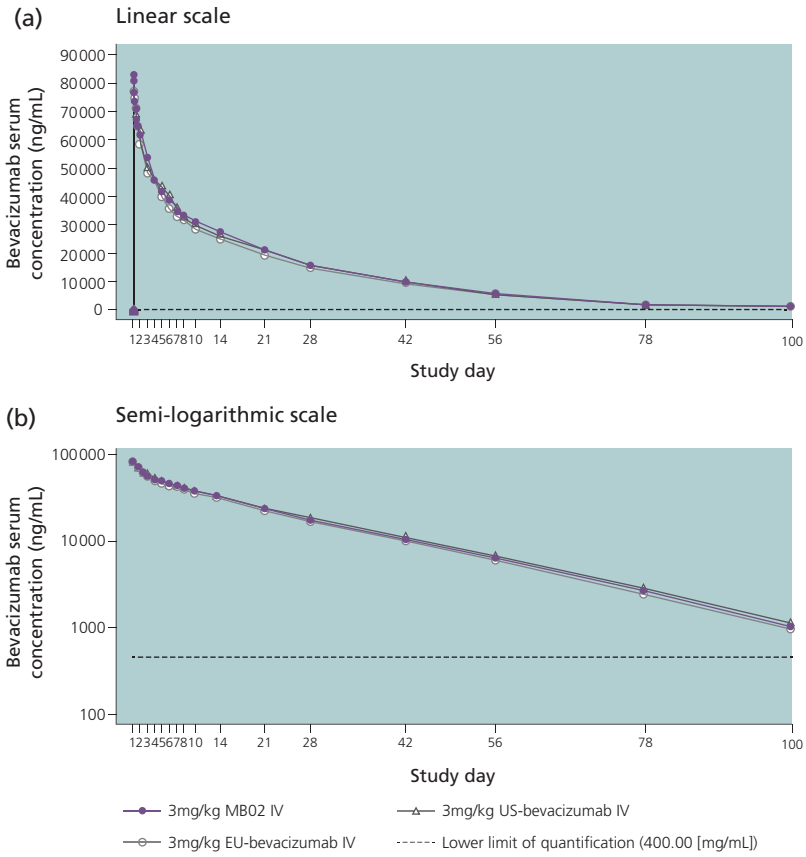

Figure 3.5 Arithmetic mean serum concentration profiles of bevacizumab over time (pharmacokinetic population). (a) Linear and (b) semi-logarithmic scale of mean serum concentrations over time of MB02, EU-bevacizumab, and US-bevacizumab. US, US-licensed; EU, European-approved; IV, intravenous.[18] Adapted from Sinn et al., 2022.

conventional statistical difference is usually set at $p \leq 0.05$. Given this error rate of 0.05, over the long run, you expect to make a type I error once out of every 20 tests (1/20=0.05).

Clinical trials for biosimilars are sometimes called Phase III-like trials or confirmatory clinical studies. The aim is to demonstrate similar efficacy and safety to the originator. The endpoint is usually

equivalence, showing that differences in response to the treatments are clinically unimportant. The first step is to define the expected outcome for the original reference biologic, then the specific range of clinically acceptable differences, called the equivalence margin. Equivalence is demonstrated when the entire confidence interval (CI) for the primary endpoint falls within the prespecified upper-lower equivalence margins (Figure 3.6).[19]

The study design, endpoints, and patient population in a clinical comparability study of a biosimilar drug may differ from those in the original trial of the reference product. However, the EMA recommends that some endpoints used for the reference product be included to support the comparability exercise.[20] The aim is to show comparability in the most sensitive clinical and PD endpoints rather than recreate the pivotal clinical trial of the originator reference drug. Table 3.2 provides specific details on the requirements.

The only major difference between the biosimilar pathway and the protocol following a manufacturing change is that PK, efficacy, and safety trials are required for all biosimilars in at least one

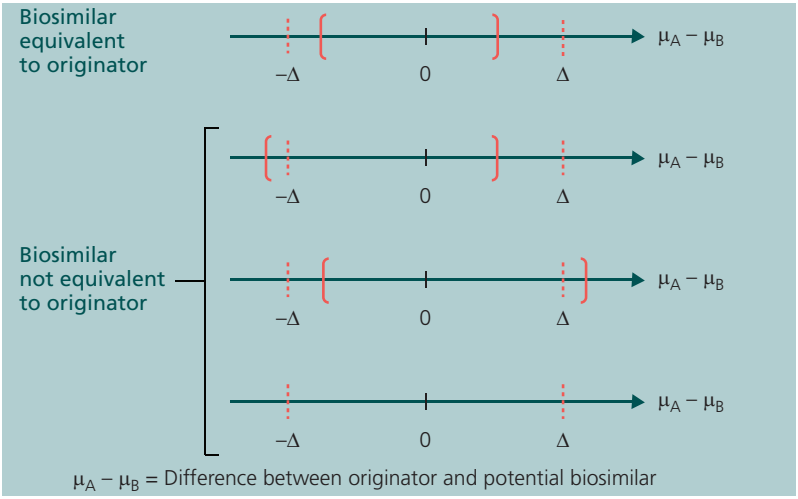

Figure 3.6 Testing for equivalence – potential results. Adapted from Isakov et al., 2016.[19]

TABLE 3.2

Regulatory requirements for a biosimilar approved in Europe

Analytical characteristics	
Primary amino acid sequence	Must be identical to the reference product
Potency	Must match the reference product
Route of administration	Must match the reference product, but the drug delivery device used can be different
Higher order structures, post-translational modifications and other potential variants	Must be as similar as possible to the reference product, with adequate analysis to ensure no effect on efficacy, safety or immunogenicity
Clinical study comparators	
Randomized comparative human studies	Stepwise approach: PK, PD (if feasible), clinical efficacy and safety using equivalence design. Efficacy trials intended to 'confirm comparable clinical performance' of biosimilar and reference. Clinical comparability of the biosimilar with its reference product must be demonstrated in at least one indication
Pharmacodynamics	Combine with PK studies where a clinically relevant PD endpoint is available; otherwise, non-clinical evaluation is required
Efficacy	Highly sensitive, dose-comparative PD studies may be sufficient; otherwise, at least one adequately powered equivalence trial
Safety	At least one adequately powered equivalence trial
Immunogenicity	Must be assessed in human clinical trials

Adapted from Dorner et al., 2013[21] and EMA 2014.[20,22]

indication (see next section); these studies must include evaluation of immunogenicity, which is difficult to predict without human studies. In contrast to originator drugs, which require pivotal clinical trials to gain new approved indications, biosimilars may gain approval by extrapolating the equivalence demonstrated in one approved indication to another. Clinical studies are required for additional indications if the approved indications have different MOA or mechanisms of toxicity that could suggest a potential risk to drug safety or efficacy.[7]

Example of a clinical confirmatory study for a therapeutic cancer biosimilar. In the example of the first trastuzumab biosimilar evaluated by the US and European regulators (MYL-Her-3001), the developer agreed on the trial design with the US FDA (ClinicalTrials.gov, NCT02472964). The primary efficacy endpoint was the overall rate of response (ORR) to combination chemotherapy and trastuzumab in patients with metastatic breast cancer. Patients needed to have secondary tumors visible on cross-sectional imaging scans. Tumor shrinkage in response to anticancer treatment is usually a good indication of treatment activity. Furthermore, to reduce the risk of bias, CT scans can be evaluated by a control pool of radiologists using validated response measurement tools such as the RECIST criteria.

The expected ORR to the reference trastuzumab was estimated by a meta-analysis of ORRs from previous randomized trials. The equivalence margin was set in consultation with the US regulator as a two-sided 90% CI for the ratio of ORRs at 24 weeks from the start of treatment. Equivalence was prespecified if the CI was completely within the equivalence range of 0.81 to 1.24. This US guidance concurs with the European guidelines, which state that "equivalence margins should be between 80 and 125% of the expected outcome for the reference biologic". The trial results, summarized from the European public assessment report (EPAR) in Table 3.3, reported a 90% CI between 0.974 and 1.211, with the data within the prespecified limit. Based on the totality of comparative data, MYL-Her-3001 was approved as the biosimilar Ogivri™ in the USA and Europe.

Validation of the trial approach was gained through long-term follow-up of the trial that enabled the early response data at 24 weeks to be compared with clinical data when the median survival had

TABLE 3.3

Primary efficacy results for reference trastuzumab and MYL-HER-3001/Ogivri™: ORR and ratio of best ORR at week 24 (ITT1 population; Study-MYL.Her-3001)

Response		MYL-1401O + taxane (N = 230)	Herceptin + taxane (N = 228)
Complete response (CR)	n (%)	3 (1.3)	0 (0.0)
Partial response (PR)	n (%)	157 (68.3)	146 (64.0)
Stable disease (SD)	n (%)	48 (20.9)	49 (21.5)
Progressive disease (PD)	n (%)	9 (3.9)	20 (8.8)
N/A	n (%)	13 (5.7)	13 (5.7)
Overall response rate	n (%)	160 (69.6)	146 (64.0)
90% CI		(64.57, 74.56)	(58.81, 69.26)
95% CI		(63.62, 75.51)	(57.81, 70.26)
Ratio MYL-1401O:Herceptin		1.09	
90% CI		(0.974, 1.211)	
95% CI		(0.954, 1.237)	

CI, confidence interval; ITT, intent-to-treat; N, number of patients in treatment arm; n, number of patients with data available; N/A, not applicable.
Source: EMA.[23]

fallen below 50% (Figure 3.7), which confirmed no clinically significant difference in the clinical events of time to progression or overall survival (OS).[23]

Since the aim is not to demonstrate the clinical benefit of the biologic, but to exclude a difference in efficacy, safety, or immunogenicity, readers will not be surprised to hear that there is no uniform clinical trial design for biosimilars of trastuzumab.

Extrapolation of indications. Central to this pathway is the demonstration that the biosimilar is *essentially the same as* the reference biologic, such that there are no significant clinical differences between the biosimilar and the reference biological product. However, it is not

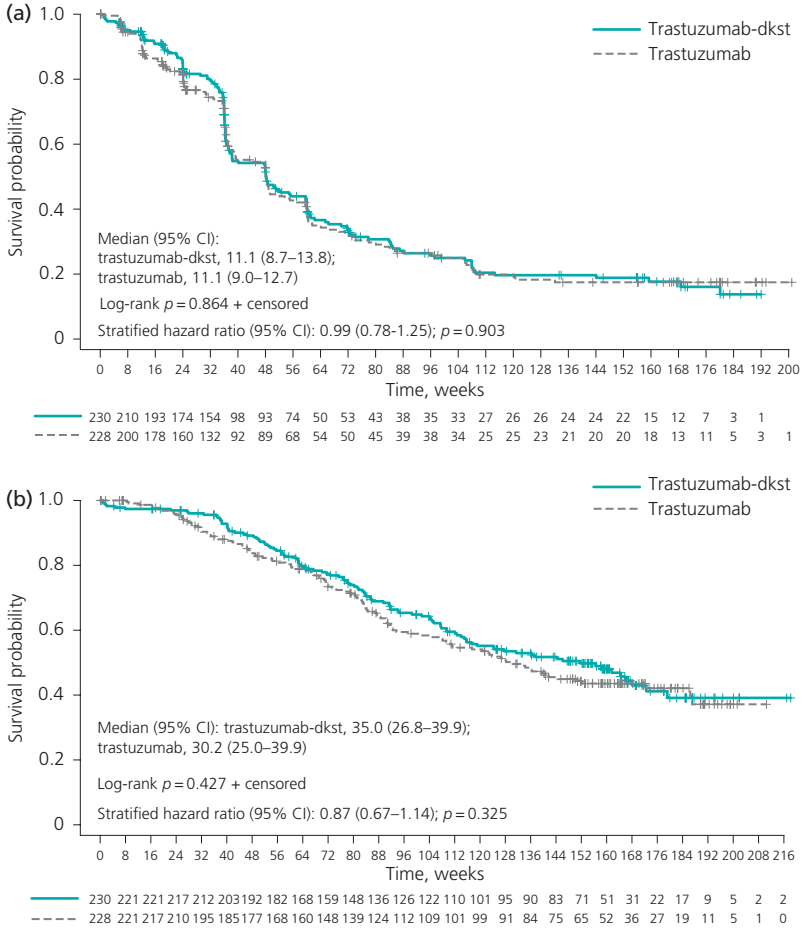

Figure 3.7 Long-term clinical efficacy results from the comparative clinical study of reference trastuzumab and MYL-Her-3001/Ogivri™ in patients with metastatic breast cancer. Endpoint (a) progression-free survival and (b) overall survival.[24] Adapted from Rugo et al., 2021.

necessary to demonstrate safety and efficacy across all the indications of the originator brand based on the understanding that if the drug has the same structure, function, and immunogenicity, it can be used to treat the same indications that share the same mechanism of action.[25]

The clinical study will likely involve the most sensitive patient group and study endpoint(s),[25] selected in discussion with regulators.

In the example of biosimilars of trastuzumab, regulators permitted studies in different indications, with some developers opting to use the setting of metastatic breast cancer and others neoadjuvant treatment of early breast cancer, summarized in Table 3.4. The most frequent indication by volume is likely to be neither of these indications, but the use of adjuvant post-operative trastuzumab. Therefore, at launch, the comparability of a biosimilar with its reference product may have been demonstrated in only one of the reference product's indications, but these data have been 'extrapolated' to justify approval in others. For trastuzumab, this would also include treating HER2-overexpressing gastric cancer. Further data may be required to demonstrate comparability if, for example, the drug has multiple sites of action, particularly if these have different relevance in different indications or if there are differences between indications in terms of efficacy, safety or immunogenicity.[20]

TABLE 3.4

Comparative efficacy trials used to demonstrate equivalence for biosimilars of trastuzumab approved by the European Committee for Medicinal Products for Human Use to September 2023*

Biosimilar identifier	Developers	Trial settings
Ogivri	Biocon/Mylan	MBC
Herzuma	Celltrion Healthcare	MBC
Kanjinti	Amgen/Allergan	EBC
Ontruzant	Samsung Bioepis	EBC
Trazimera	Pfizer	MBC and additional EBC
Zercepac	Accord Healthcare	MBC
Herwenda/EG12014	Sandoz and EirGenix	MBC

*Since the aim is to demonstrate pharmacodynamic equivalence, studies can include any setting where the shrinkage or disappearance of the cancer can be recorded. Settings include metastatic breast cancer (MBC) and the neoadjuvant treatment of early breast cancer (EBC).

Since the biosimilar comparability study is directed to explore the 'sameness' of the drug, there is no expectation that the study will show the agent's overall efficacy, risks and benefits. This explains why the indications, warnings and contraindications set out in the summary of product characteristics (SPC) (or prescribing information) for the biosimilar will be drawn from the SPC of the originator. The public assessment report (PAR) will indicate whether indications have been approved based on extrapolation or data from comparative clinical studies.[25]

Public assessment reports. Before market authorization, a biosimilar developer must submit an application to regulators detailing the biosimilar development process and comparability studies demonstrating biosimilarity, including analytical and functional comparability, PK, clinical comparability and immunogenicity.[26]

These data are used to produce a PAR detailing scientific conclusions made by the regulatory committee after reviewing the application and determining whether the application is approved or not. Confidential information used during the scientific assessment is removed before publication. In Europe, this report is known as the EPAR issued by the EMA, while in the USA it is simply a PAR issued by the FDA. A PAR comprises regulatory documents covering the initial scientific evaluation and when major changes are introduced (Table 3.5). The PAR is maintained to provide the latest regulatory information on a biosimilar.[26]

EPARs for all centrally authorized biosimilars can be viewed on the EMA website, while PARs of FDA-approved biosimilars can be viewed on the FDA website under the 'Biosimilar Product Information' page.

Safety. Safety data for a biosimilar are likely to be limited at the time of launch;[9] however, experience to date indicates that the adverse event profiles of biosimilars match those of their originators.[13] Indeed, safety monitoring within the EU has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicines over the 10 years since the introduction of biosimilars.[2] The comparability studies performed on biosimilars mean that the risk of new or severe adverse events (type 2) is likely to be lower than with a novel biological agent.[9]

TABLE 3.5

The four sections containing different components of the EPAR[26]

Section	Type of information
Overview	Public-friendly overview in question-and-answer format
Authorization details	Key details about the product and the marketing authorization holder
Product information	Package leaflet and SPC; labeling; list of all authorized presentations; pharmacotherapeutic group; therapeutic indications
Assessment history	PAR for the initial authorization; PAR(s) for any variation concerning major changes to the marketing authorization; orphan maintenance assessment report or withdrawal assessment report (as of 17 January 2018); tabulated overview of procedural steps taken before and after authorization

Pharmacovigilance. Clinical studies on a biosimilar prior to authorization are generally limited, and, as for any new drug, post-marketing surveillance is required to enable the identification of any rare adverse effects.[20] Biosimilars are subject to the same degree of post-approval pharmacovigilance as the originator biologic. Product naming will be crucial, since biosimilars and originators will share the same international non-proprietary drug name (INN). In Europe, reports of adverse drug reactions (ADRs) must include the biologics brand name and batch number. In 2019, the FDA updated its guidelines on biosimilar nomenclature to incorporate four lowercase letters after the biosimilar INN as a biologic qualifier. This update aims to promote accurate identification and facilitate pharmacovigilance by ensuring proper traceability.[27]

Special reporting requirements may apply to biosimilars, even though they are versions of established originator brands, and they may likewise be assigned a black warning triangle requiring prescribers

to report any ADRs. A risk minimization plan is also a requirement for marketing a biosimilar;[25] details are provided in the EPAR.

Real-world studies

Observational real-world pharmacoepidemiological data may be available for the originator biologic; the EMA encourages biosimilar manufacturers to participate in these studies, if available, or to begin a new program.[20]

Biosimilars in the USA. In the USA, the first copies of biologic reference drugs were approved through a comparability pathway as complex generics – human growth hormone Omnitrope® (Sandoz) in 2006 and Enoxaparin-M-Enoxaparin™ (Momenta/Sandoz) in 2010. Without the regulatory description of 'biosimilar', the US versions of these drugs did not attract the negative position statements of clinician associations that were seen in Europe.

Further biosimilar approvals then stalled until new legislation was passed to create a separate biosimilars approval pathway; one section of the 2010 Patient Protection and Affordable Care Act permitted biosimilars but also potentially delayed their market entry by extending data exclusivity for original reference drugs to 12 years and imposing controversial disclosure requirements on biosimilar makers.

The scientific steps to approval are directly analogous to those in Europe; however, the US pathway distinguishes between 'biosimilars' and 'interchangeable biosimilars'; only the latter have regulatory approval for potential brand substitution by dispensing pharmacists. For a biosimilar to be designated as interchangeable, proof is required that it will have the same expected clinical results in any given individual patient. Furthermore, if the medicine is administered more than once, the 'interchangeable' product should demonstrate comparable safety and efficacy when switching between the biosimilar and the reference product. This implies that post-marketing data from an already approved biosimilar will be required to gain interchangeable status. The FDA's core requirements for interchangeability were published in 2019. These requirements have been updated and refined but no significant changes have been made.

Automatic substitution of drugs by pharmacists is believed to create price competition between manufacturers that will reduce costs and

promote patient uptake, analogous to the effect of generic substitution with small-molecule drugs. One year of marketing exclusivity for the first approved interchangeable biosimilar is suggested in the USA to encourage this process.

The FDA has emphasized that the closer the analytical match of a biosimilar to the variation observed in the original reference drug, the less the requirement for clinical trial data. Where there is little difference that could affect predicted clinical outcomes, the proposed biosimilar is described as having 'fingerprint-like' similarity. The greater any differences, the greater the requirements for demonstrating equivalence in clinical trials.

Key points – how are biosimilars approved in Europe and the USA?

- The quality attributes – chemical, physical, and biological properties – of a biologic must be within a developmental corridor that defines the acceptable upper and lower limits of the marketed product.
- The evidence required for approval of biosimilars is greater than that for generic versions of small-molecule drugs.
- Central to the EMA 'biosimilar pathway' is the demonstration that there are no significant clinical differences between a biosimilar and its reference biologic, based on analytical, preclinical, and clinical data.
- Safety monitoring in the EU over the 10 years since the introduction of biosimilars has not identified any relevant difference in the nature, severity, or frequency of adverse effects between biosimilars and their reference medicines.
- Comparability studies mean that the range and severity of potential adverse events can be predicted from the experience with the originator reference biologic gained over many years of clinical use.
- Biosimilars are subject to the same pharmacovigilance as their reference biologic, including special report requirements (black triangle; risk minimization plan).

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Pharmacology

4 Biosimilars in Europe: from regulatory approval to clinical practice

HEALTHCARE

As at January 2024, 88 authorized biosimilars were listed on the European Medicines Agency (EMA) Medicines page, covering 25 reference biologics (Table 4.1). Since 2006, with the first approval of a somatropin biosimilar, there has been a steady increase in the number of biosimilars approved for use in the EU and an expansion in the number of first-in-class biosimilars authorized (Figure 4.1). Between 2016 and 2020, biosimilars generated more than €10 billion in savings for France, Germany, Italy, Spain, and the UK.[1] These numbers are likely to expand rapidly, with approximately 120 reference biologics expected to lose exclusivity in the coming decade.[2]

Biosimilar quality, safety, and efficacy

The entry of biosimilars into the European market has made a positive impact through lowering costs and expanding access. Europe has been at the forefront of regulating biosimilars, having established a

TABLE 4.1

Active substances with authorized biosimilars (indicated in brackets) that are listed on the EMA Medicines page as of July 2024

Adalimumab (10)	Insulin glargine (2)
Aflibercept (1)	Insulin lispro (1)
Bevacizumab (8)	Natalizumab (1)
Denosumab (2)	Omalizumab (1)
Eculizumab (2)	Pegfilgrastim (8)
Enoxaparin sodium (1)	Ranibizumab (4)
Epoetin alfa (3)	Rituximab (5)
Epoetin zeta (2)	Somatropin (1)
Etanercept (3)	Teriparatide (5)
Filgrastim (7)	Tocilizumab (2)
Follitropin alfa (2)	Trastuzumab (7)
Infliximab (4)	Ustekinumab (3)
Insulin aspart (3)	

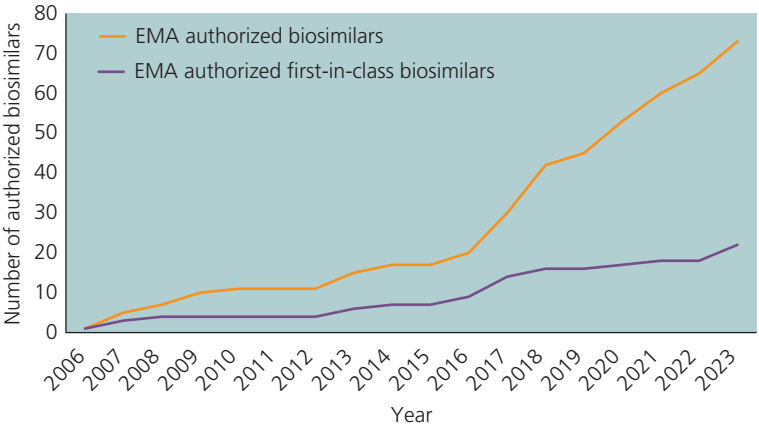

Figure 4.1 The number of biosimilars and first-in-class biosimilars authorized by the EMA since 2006. Based on the manufacturer, to avoid double counting of follow-on biologics with multiple marketing authorization applications. Based on data from EMA, 2024.

regulatory framework in 2004.[2] Based on these stringent requirements, biosimilar usage in the EU has demonstrated an excellent safety record over the past 18 years.

A large study by Kurki et al. (2021) assessed biosimilar monoclonal antibodies and fusion proteins approved in Europe before 2020. More than 1 million patient-treatment years of safety data were analyzed, with authors reporting that no safety concerns were raised. In addition, biosimilars had comparable efficacy, safety, and immunogenicity to the reference biologics.[3]

A recent study looked at bevacizumab, rituximab, and trastuzumab and analyzed post-marketing pharmacovigilance data obtained from the EudraVigilance database for reference biologics and biosimilars between 2021 and 2022 (Figure 4.2). The results demonstrated that adverse drug reactions (ADRs) in biosimilars were non-serious and consistent with the safety profiles of reference biologics.[4]

Extrapolation. Extrapolating safety and efficacy data generated based on one indication into different indications is a common approach when approving biosimilars. Extrapolation is also used

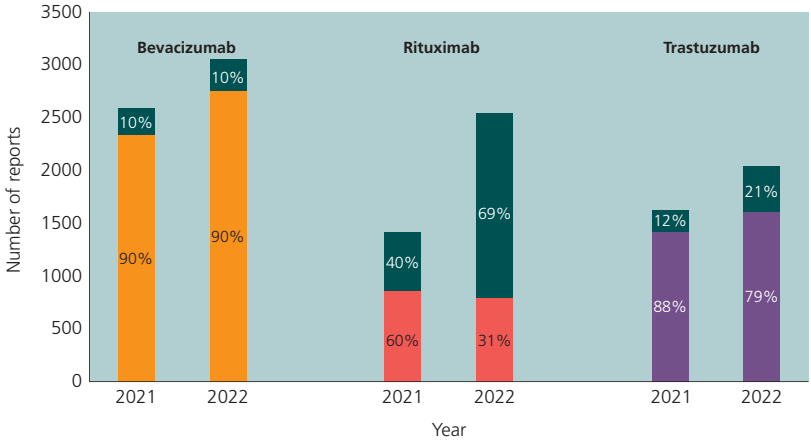

Figure 4.2 The total number of reports of adverse drug reactions for bevacizumab, rituximab, and trastuzumab biologics between 2021 and 2022. The proportion of reports from biosimilars is indicated in green. The reference biologics were Avastin® (orange), MabThera® (red), and Herceptin® (purple).[4]

for reference biologics when modifications are applied to the manufacturing process; that is to say, the same scientific principles are used when assessing biosimilarity and showing comparability after a change in the manufacturing process of a reference biologic.[5] Given the importance of extrapolating biosimilar data, eight of the nine EU product-specific guidelines feature a section dedicated to extrapolation. Furthermore, extrapolation is covered in a specific section of the European public assessment report (EPAR).[6]

Variable uptake of biosimilars: the European experience. Europe has seen a dramatic improvement in the overall uptake rate of biosimilars 1 year post-entry, increasing from 40 to 75%. While approval of biosimilars mostly happens centrally at the EU level, the guidance around using biosimilars is down to the member states.[2,7] In 2022, 40% of member state medicine agencies did not have available information on biosimilars or their usage, undoubtedly contributing to differences in biosimilar uptake (Figure 4.3).[8] Low usage is linked to a limited understanding of biosimilars, particularly

	HOSPITAL									MIXED	INSULINS	
	infliximab	etanercept	rituximab	rituximab IV	trastuzumab	trastuzumab IV	pegfilgrastim	bevacizumab	teriparatide	adalimumab	Insulin Glargine	Insulin Lispro
Germany	83%	80%	86%	93%	83%	94%	56%	93%	45%	74%	16%	6%
France	84%	50%	75%	97%	45%	98%	79%	99%	53%	41%	28%	0%
Italy	95%	78%	88%	99%	79%	99%	85%	92%	71%	80%	15%	11%
Spain	82%	53%	73%	96%	69%	95%	87%	78%	60%	63%	18%	0%
Netherlands	90%	44%	97%	99%	84%	100%	95%	94%	68%	66%	34%	16%
Denmark	99%	93%	86%	100%	95%	99%	100%	99%	17%	97%	29%	0%
Finland	98%	50%	93%	100%	54%	100%	66%	90%	16%	58%	4%	44%
Norway	99%	94%	94%	199%	92%	100%	98%	91%	75%	92%	22%	5%
Poland	100%	68%	99%	99%	38%	100%	100%	96%	0%	99%	28%	27%

Figure 4.3 An illustration of the uptake of biosimilars across Europe.[8] Source: IQVIA, 2022.

given that the approval process for biosimilars differs from the reference biologic.[2]

Clinician confidence. Gaining the confidence of clinicians to start new patients on biosimilars and switch patients during treatment is crucial to creating a competitive market. However, studies show that there is some way to go in building this confidence with biosimilars. Barriers to biosimilar use include:[9]

- a lack of understanding and trust regarding biosimilars by clinicians and patients
- a lack of financial incentive
- prescribing shifts to new alternatives
- problems associated with the tendering system
- non-coherent policy.

Lack of confidence and knowledge. A survey conducted in 2021 among physicians and pharmacists in Spain found that while a positive perception of biosimilars was reported, the main barrier to usage was a lack of confidence and knowledge, particularly relating to extrapolation, interchangeability, substitution and switching. Furthermore, the availability of biosimilar types and brands in hospitals varied and was affected by organization policies, practices and preferences.[10] In Austria, only 45.7% of Viennese physicians reported being familiar with biosimilars. Furthermore, only 33.8% of healthcare professionals expressed no concerns about biosimilars.

The main concerns raised related to switching (26.9%), lower efficacy (11.4%) and poor quality (7.4%). These results are reported to be in line with the European average for understanding and trust of biosimilars.[11]

Lack of financial incentive. For biologics such as disease-modifying anti-rheumatic drugs infliximab, etanercept and adalimumab, used in rheumatoid disease (and other inflammatory conditions), patients are typically treated for 5 years or longer, which, for a healthcare system procuring drugs through annual competitive tenders, offers multiple opportunities to lower the prescription costs for individual patients. If, however, clinicians are unwilling to switch patients to biosimilars, pharmacies are forced to stock various brands of the same drug and, therefore, forgo much of the potential economic gain.

Interventions aimed at improving trust and understanding. The EU and member states have undertaken various interventions to encourage biosimilar uptake by strengthening trust and understanding of biosimilars among healthcare workers. In 2023, the EMA released a joint EMA-Heads of Medicines Agencies statement on interchangeability in which it explained the scientific rationale supporting the interchangeability of biosimilar medicines in the EU to expand patient access to biosimilar medicines.

The European Specialist Nurses Organisation (ESNO) is also actively involved in education initiatives designed to support nurses in understanding biosimilars. In 2022, ESNO published the second edition guide titled 'Switch Management between Similar Biological Medicines', which covers all aspects of biosimilar use.

Physicians are the primary target of education policies focusing on clinical guidelines and prescribing recommendations. Furthermore, efforts to change prescribing behavior have been implemented to encourage biosimilar uptake, such as introducing quotas or profit-sharing of savings.[1]

Non-coherent pricing policies. Once marketing authorization is given by the European Commission, reimbursement is agreed upon at the national level before the biosimilar becomes available to patients in that member state.[12] However, several pricing policies are in place throughout Europe (Table 4.2).[13,14]

TABLE 4.2

An overview of 2022 pricing and reimbursement policies in Europe

Country	EPR	Biosimilar price link	Reimbursement list(s)	RPS	INN prescribing	Biosimilar substitution
Austria	Yes	Yes	Yes	No	No	No
Belgium	Yes	Yes	Yes	Yes	No	No
Czech Republic	Yes	Yes	Yes	Yes	Yes	Yes
Denmark	Yes	No	Yes	No	No	No
Finland	Yes	Yes	Yes	No	Yes	No
France	Yes	Yes	Yes	No	No	Under implementation
Germany	Yes	No	Yes	Yes	No	Under implementation
Greece	Yes	Yes	Yes	Yes	Yes	No
Hungary	Yes	Yes	Yes	Yes	Yes	Yes, for selected biologics
Ireland	Yes	Yes	Yes	No	No	No
Italy	Yes	Yes	Yes	No	Yes	No
Netherlands	Yes	No	Yes	Yes	Yes	Yes

CONTINUED

TABLE 4.2 CONTINUED

An overview of 2022 pricing and reimbursement policies in Europe

Country	EPR	Biosimilar price link	Reimbursement list(s)	RPS	INN prescribing	Biosimilar substitution
Norway	Yes	Yes	Yes	Yes	Yes	Yes
Poland	Yes	Yes	Yes	No information	Yes	Yes
Portugal	Yes	Yes	Yes	No	Yes	No
Slovakia	Yes	Yes	Yes	No information	Yes	No
Spain	Yes	Yes	Yes	Yes	No	No
Sweden	No	No	Yes	No	No	No
Switzerland	Yes	Yes	Yes	No	Yes	No
United Kingdom	No	No	Yes	No	No	No

EPR, external price referencing; INN, international non-proprietary name; RPS, reference price system.
Adapted from Leopold et al. 2023[13] and Schneider 2024.[14]

Measuring impact. Scientific evaluation of these interventions can provide valuable insight into the impact of these measures and guide policymakers on future interventions. One such assessment was conducted in Belgium to assess intervention measures to increase the usage of two different biosimilars in the hospital setting (filgrastim and epoetin). Interventions included prescription targets for biosimilars, monitoring of hospitals on adequate tendering and information campaigns on biosimilars. Such interventions were variable and limited in increasing the uptake of biosimilars.[9]

Switching between biosimilars and reference biologics is a major concern among clinicians, in part due to the extrapolation of data for biosimilars onto other indications.[10,11]

This has been extensively studied, and no safety concerns have been identified.

A systematic review and meta-analysis assessed 31 switch treatment periods (STPs) involving 21 biosimilars. The report indicated that no difference in the safety profile, including treatment discontinuation, serious adverse events and death, was detected for STPs. Furthermore, no difference in the incidence of ADA and neutralizing antibodies was found between patients who switched and those who did not.[15]

An example of switching has been with adalimumab, where patients have been switched from the reference biologic (Humira®) to the biosimilar SB5 (Imraldi®). The biosimilar has been approved for all indications listed for the reference biologic; however, only a single indication was evaluated using a randomized clinical trial to assess the switch between the reference biologic and the biosimilar.

To better understand the clinical outcomes of switching between adalimumab biologics, the non-interventional, single-cohort, real-world PROPER study (NCT04089514) was conducted in 2019, looking at patients with immune-mediated inflammatory diseases covering multiple indications across six European countries. The real-world data generated from this study demonstrated that the switch between biologics was well tolerated and safe. Furthermore, disease control was maintained, and 75% of patients continued to receive the biosimilar 48 weeks post-switch. No difference was observed in disease outcomes between patients who switched and patients who remained on the reference biologic.[16]

Pharmacovigilance. The EudraVigilance database, operated by the EMA, is responsible for collecting data on all suspected ADRs to medicines authorized in the European Economic Area, and it represents one of the largest spontaneous reporting systems in the world.[17] For biologics, ADR reports must include the brand name and batch number to assist with traceability.[18]

Overall, accurate reporting has been observed in Europe, with 91.5% of all ADR reports clearly stating the precise biologic, and the introduction of biosimilars has not impacted reporting accuracy.[19] However, ADR reports featuring the biologic brand name and batch number have been reported to be as low as 5%, which is cause for concern.[18] A similar observation has been seen in the UK, where the recording of brand names during routine hospital processes varied between 79% and 91%. The capturing of batch numbers was found to be lower at between 38% and 58%.[20]

Naming policy differences between the EU, USA, and Japan. Various naming conventions for biosimilars have been adopted to aid traceability and pharmacovigilance (Table 4.3). Biosimilars in the EU are distinguished by brand name or international non-proprietary name (INN) followed by the marketing authorization holder in cases where no brand name is used. In Japan, biosimilars are identified by the INN, followed by the distinguisher 'BS' and a sequential number based on each new approval for that INN.[21] The US naming incorporates a four-letter suffix at the end of the INN to distinguish between biosimilars.[22]

TABLE 4.3

An example of the naming policies used for bevacizumab in the EU, USA and Japan

INN	Company	EU	USA	Japan
Bevacizumab	Pfizer	Zirabev	Zirabev (bevacizumab-bvzr)	Bevacizumab BS 1

Key points – biosimilars in Europe: from regulatory approval to clinical practice

- There are 88 authorized biosimilars in the EU and this number is expected to climb with 120 reference biologics losing exclusivity in the coming decade.
- Biosimilar usage in the EU has demonstrated an excellent safety record over the past 18 years.
- Biosimilars are authorized at the EU level while guidance around usage is down to the member states.
- Clinician confidence is crucial in starting new patients on biosimilars and switching patients during treatment.
- The EU, member states and organizations are actively encouraging biosimilar uptake through pricing and reimbursement policies and by strengthening trust and understanding among healthcare workers.
- The EMA has released a statement in support of biosimilar interchangeability as a means of expanding patient access.
- The reporting of ADRs must include the brand name and batch number to assist with traceability.
- Biosimilars in the EU are distinguished by brand name or INN followed by the marketing authorization holder in cases where no brand name is used.

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Pharmacology

5 Intended copy biologics: what are they and does it matter?

HEALTHCARE

Biosimilars are follow-on biologics which follow a unique regulatory approach designed to address the requirements of biologics as opposed to small-molecule generics. The approach to assessing biosimilars involves stringent comparability assessments to demonstrate that the biosimilar is clinically equivalent to the reference biologic without compromising efficacy and safety. Australia, Canada, the EU, Japan and the USA have biosimilar regulatory pathways, and the WHO has established recognized standards.[1]

In predominantly low- and middle-income countries (LMICs), regulations concerning biosimilars have either only recently been established or do not meet WHO standards (Figure 5.1). This has allowed intended copy biologics (ICBs) that were not developed to biosimilar standards of the WHO to be approved.[1] As such, ICBs can differ in structure from the reference biologics in that efficacy and safety are different. Furthermore, ICBs can be lower in price than biosimilars.[2] Some LMICs still approve biosimilars and ICBs, which can create confusion. This can be further exacerbated when ICBs are incorrectly marketed as biosimilars, leading to a lack of trust in biosimilars in LMICs and limited adoption.[3]

To differentiate this class of medicines, these are usually not called biosimilars by the relevant medicines regulators; for example, in India, they are called *Indian similar biologics* (ISBs), but also have been termed *bio-generics*, *bio-copies*, *non-comparable biologics*, *biomimics, non-regulated biologics*, *non-innovator biologics* and *non-biosimilars*.[1,3] By 2023, 67 biosimilars were approved in Australia, Canada, the EU, Japan and the USA, compared to 237 ICBs not approved as biosimilars in these countries.[1]

Intended copy biologics – a lower-cost solution that evolved outside Europe. With production costs and the requirement to deliver a commercial return on investment much the same worldwide, the only realistic way to deliver biologics at prices citizens in LMICs can afford is to reduce development costs.[4,5] This likely explains why a range of alternative regulatory requirements for follow-on biologics have evolved in many LMICs. In some countries, approval is still based on generic regulatory pathways for small-molecule drugs.[3]

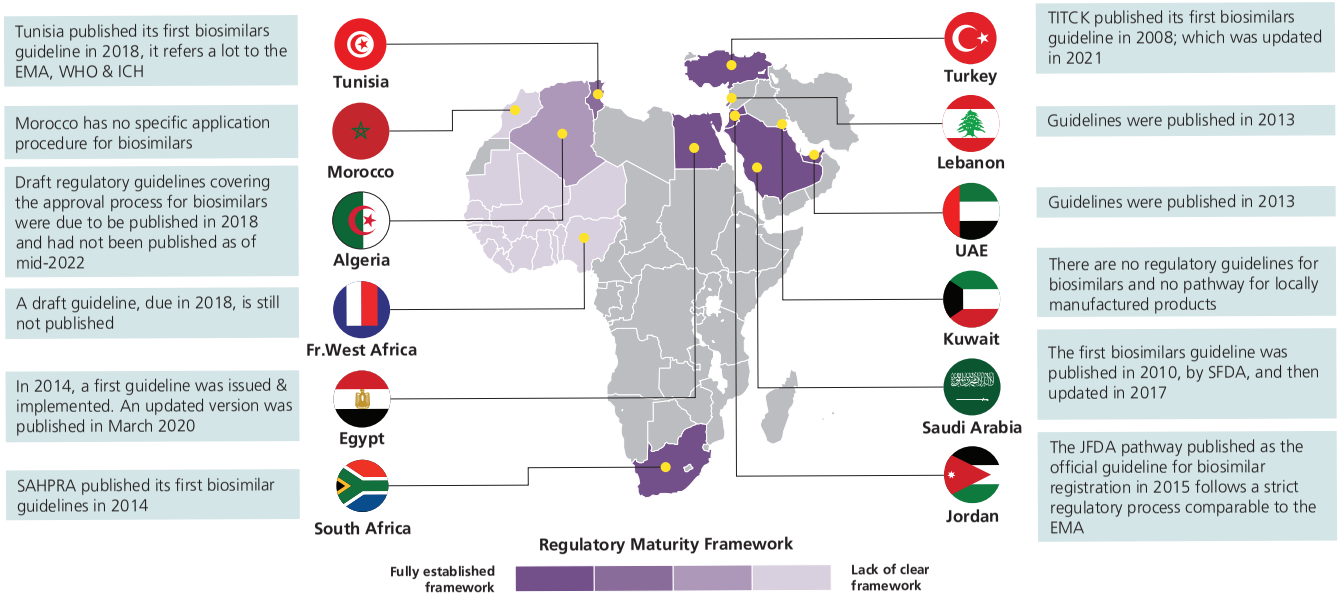

Figure 5.1 Biosimilar regulations in the Middle East and Africa as of June 2023.[6] EMA, European Medicines Agency; ICH, International Council for Harmonisation; JFDA, Jordan Food and Drug Administration; TITCK, Turkish Medicines and Medical Devices Agency; SAHPRA, South African Health Products Regulatory Authority; SFDA, Saudi Food and Drug Authority; UAE, United Arab Emirates; WHO, World Health Organization.

In India, the first locally produced biologic approved and marketed by the Central Drugs Standard Control Organization (CDSCO) was a hepatitis B vaccine, Biovac-B™ (Wockhardt). It was authorized in 2000 before the European biosimilar pathway was announced.[7,8] By 2022, there were 78 follow-on biologics approved in India, of which 71 were ISBs, and the remaining seven were biosimilars, which were also approved in Australia, Canada, the EU, Japan and/or the USA.[1]

The first follow-on biologics in India were approved as novel medicines and were classified as ISBs. Such approval went through an abbreviated route that relied on limited safety and efficacy data to keep production costs low and make the product affordable in Indian terms.[9] As such, these products could out-compete European biosimilar prices – some ISBs control 75% or more of the Indian domestic market.[10]

Two trastuzumab ISBs demonstrate how a regulatory step can be underpowered compared with the WHO standards. The first is the requirement for equivalent functional activity between a proposed biosimilar and the reference biologic for all potential mechanisms of action (MOA). Trastuzumab works through two mechanisms: Her2 receptor binding that triggers an anti-proliferation response and a second mechanism of antibody-dependent cellular cytotoxicity (ADCC), yet the regulations call for only equivalence in the anti-proliferation assay. This was underlined by product drift of the originator brand trastuzumab, which reduced ADCC activity and led to a significantly diminished tumor response.[11–13]

Compared with Europe, the second area of shortcoming is the statistical consideration for the confirmatory clinical trial. Smaller trial participant numbers mean less chance of discovering a statistically significant difference in efficacy and fewer participants exposed to the new biologic with which to assess drug safety. Before the 2016 update to Indian guidelines on similar biologics, no specific trial size or endpoint was specified, but after 2016 the regulations explained, "Phase 3 data should generally be obtained on at least 100 patients primarily to confirm the efficacy and safety of the drug in Indian patients".[14]

In consequence, trials tended to be sized to the minimum; for example, trial CTRI/2014/05/004605 for an ISB of trastuzumab enrolled 102 participants in an open-label study randomized 2:1 and led to the approval of that medicine in 2015 by the CDSCO.[15]

A second example was trial CTRI/2013/04/003549 with 105 participants, again in open-label design, for another trastuzumab ISB that the CDSCO approved in 2015.[16] Small patient cohorts led to criticism of ISB regulations by the Indian Parliamentary Standing Committee on Health and Family Welfare, which oversees the CDSCO.[17,18] In contrast, an average of 669 participants had enrolled in confirmatory efficacy and safety trials for the seven trastuzumab biosimilars approved in Europe up to January 2024 (Table 5.1).

As a way to demonstrate the statistical impact of increased participant numbers in biosimilar equivalence trials, here is a theoretical example. Suppose you expected a response rate of 50% to reference brand trastuzumab, and there is no difference between the reference and follow-on biologic treatment (50% response in both groups). In that case, a European-size trial of 669 patients can predict that the limits of a two-sided 90% confidence interval (CI) will exclude a difference of more than 13%. In contrast, with only 100 patients, the limits of 90% equivalence that could be detected would be 2.5 times wider at more than 23%.[19,20]

While ICBs may be safe and effective medicines, the standards used for approval are demonstrably different to those used in European-approved biosimilars. As such, conclusions about the overall biosimilar safety and efficacy levels in Europe are not automatically translatable.[8] Below is a look at the stepwise approval process for biosimilars contrasted with examples of ICB approvals which use less stringent requirements and how this curtails their use.

The stepwise approval of biosimilars and ICBs compared and why this matters. By definition, an ICB misses out or underpowers one or more steps of the biosimilar regulatory pathway. These regulatory steps can be followed through the European patient assessment reports (EPARs) and in the Briefing Documents for Drug Advisory Assessment Committee Meetings of the US Food and Drug Administration (FDA); both are publicly available and accessible from the respective regulators' websites.[21,22] Crucially, there is not one standard clinical assessment design for all biologic medicines, as the regulatory aim is to discover if the two versions of the same drug differ sufficiently to create a significant difference in clinical performance. Instead, regulators and developers discuss the requirements on a drug-by-drug basis. The

TABLE 5.1

Comparison of the participant numbers and designs of the efficacy and safety trials of trastuzumab*

Regulatory authority	Follow-on drug identification	Trial		
		Participant numbers	Registration identification number	Design
CDSCO	Zydus[15]	102	CTRI/2014/05/004605	Open-label study, randomized 2:1
CDSCO	R-TPR-016[16]	105	CTRI/2013/04/003549	Open-label study, randomized 1:1
EMA	CT-P6	549	NCT02162667	Double-blind study, randomized 1:1
	ABP 980	596	NCT01901146	
	Myl1401O	500	NCT02472964	
	SB3	875	NCT02149524	
	PF-05280014	707	NCT01989676	
	HLX02	649	NCT03084237	
	EG12014	807	NCT03433313	

*For two ISBs of trastuzumab approved in 2015 by the Indian CDSCO with the trials for seven biosimilars of trastuzumab approved by the EMA up to January 2024.

European Medicines Agency (EMA) produces drug-specific dossiers outlining the requirements for follow-on versions of each reference drug.[23]

Step 1: Target definition. Biosimilar developers buy multiple batches of original reference biologics, often in Europe and the USA, to map the variability of critical attributes of drug structure and function over time to define the target to copy. This provides an understanding of what will ensure the quality, safety, and efficacy of the follow-on product for the patient.

The requirement of how many batches of reference biologics to buy and over what length of time is not defined by regulators, either for biosimilars or ICBs. For example, the WHO advises that the number should only be 'several batches'.[24] The margin of error of a CI is affected by the size of the statistical sample; as the sample size increases, the margin of error decreases. Lack of adequate collection of the reference biologic from different regions over time leads to lower confidence in the target definition and hence the 'developmental corridor' of critical quality attributes. Furthermore, a small sample number of different batches of a reference biologic, compared with very few production batches of a proposed follow-on biologic, may give false confidence that the two drugs are similar simply because the CIs of the data are very wide.

Step 2: Analytical comparative quality studies. Biosimilars undergo a head-to-head comparison with the reference biologic regarding physical and chemical properties using the highest resolution orthogonal analytics.

In the case of ICBs, such analysis may not be as thorough, resulting in significant differences compared to the reference biologic. Examples include differences in primary protein structure, as with a ranibizumab ICB.[25] Differences in post-translational modifications can also occur, such as with epoetin ICBs from China, India and Korea with more glycoforms and other impurities.[26] As with a rituximab ICB, differences can also impact protein charge, which is detrimental to product stability.[27–29] Furthermore, a lack of comparability data can prevent regulators from establishing similarity with reference biologics. The Malaysian regulator, which follows WHO and EMA guidelines, has frequently cited limited availability of comparability data when assessing ICBs from other countries.[30]

Step 3: Functional comparative quality studies. In addition to analytical studies, biosimilars undergo head-to-head comparisons of biological and pharmacological activity using receptor binding studies, bioassays and, in some cases, animal studies.

A WHO 2010 biosimilars workshop showed many differences in quality between an intended copy of rituximab and the reference biologic.[31] Furthermore, a rituximab ICB has also been found to have reduced ADCC and complement-dependent cytotoxicity – two fundamental modes of action of this drug.[28,32] In another example, two filgrastim ICBs have demonstrated significantly lower or higher specific activity than the reference biologic and biosimilars.[33] ICBs for interferon from Latin America and Iran have also been found to have differences in biological potency and significant batch-to-batch variability.[34] A lack of orthogonal assessment of comparability potency in all modes of action prevents ICB performance from being predicted in extrapolated indications.

Step 4: Comparative non-clinical studies: toxicology. Biosimilars are also assessed to determine the clearance of cell debris and contaminants from the host cell or host tissue from which the biologic is extracted, and sometimes pharmacodynamic assessments in animals.

In another example involving epoetin, Thai ICBs have been found to have had high aggregate levels and contained a substantial amount of protein fragments. One such ICB had a high endotoxin level above the FDA limit.[35] A filgrastim ICB has also been found to have higher impurities and lower thermo-stability when compared to the reference biologic and biosimilars.[33] In the case of the interferon ICBs described previously, these were also shown to contain higher molecular-weight aggregates of interferon as well as adducts with human serum albumin.[36]

Step 5: Chemistry, manufacturing and controls (CMC). CMC describes the medicine's chemistry, production process, and analytical controls that keep the biologic's quality consistent over time. This step is covered by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process Q5E guidelines of 2004. These guidelines are designed to limit the 'drift' and 'step' changes in

functional and structural analyses over time and mandate that further analysis at clinical levels is required if uncertainty exists.

Etanercept ICBs have been found to have significant differences regarding their CMC, limiting the ability of that biologic to be manufactured with stable attributes over time.[37] Failure to maintain CMC can result in significant lot-to-lot variability, as has been the case for an interferon beta ICB.[36] In addition, batch-to-batch consistency may not even be demonstrated as has previously been reported for interferon alfa-2a, filgrastim and erythropoietin.[30] Regulations guiding ICBs can also be incomplete, as with the ISB 2012 regulations which did not require tests assessing the ratio of heavy chain versus light chain of the protein included in the Certificate of Analysis.[38]

Step 6: Comparative clinical studies: pharmacokinetics (PK) and pharmacodynamics (PD). Head-to-head randomized parallel or crossover clinical trials between the reference biologic and biosimilar are used to document the pharmacological action. Trials can involve healthy volunteers or require patients with the target disease.

Comparative head-to-head PK studies for ISBs produced and marketed before 2012 were not mandatory.[9] In a further example, PK analysis of a rituximab ICB demonstrated markedly different results from the reference rituximab.[39] A lack of comparable PK/PD means that dose/schedules cannot be determined for ICBs without a dose-finding study.

Step 7: Comparative clinical studies: immunogenicity. Many biological drugs are immunogenic; the presence of neutralizing anti-drug antibodies (ADA) can alter drug PK and lead to loss of efficacy at titers that may be too low to create clinical effects such as infusion reactions. Similar immunogenicity is required for biological brands to be switched mid-treatment without losing efficacy. A WHO Biosimilars Workshop has advised that a mandatory pre-approval comparative immunogenicity study should assess the incidence and characteristics (antibody titer, antibody class and subtype, neutralization potential, etc.) of any ADA in the follow-on biologic and comparator arms.

In the example of an epoetin ICB, such studies were advised to be powered to detect adverse events with a 1% or greater incidence (requiring approximately 300 patients). Since neutralizing antibodies develop over time, immunogenicity must be assessed

in patients treated for 6 to 12 months.[40] In one case, a rituximab ICB was approved using a 70-patient, two-arm PD study of chronic lymphocytic leukemia (CLL). With 35 patients exposed to the ICB, the 'n/3' rule predicted the study had sufficient power to exclude with 95% power a rate of unexpected immunogenicity of only 9% or greater.[41] Statistical calculations can determine the minimum number of patients needed to be exposed to a drug to be confident on the upper limit of immunogenicity; for example, at least 60 patients will need to be studied to be 95% certain the true rate of neutralizing anti-drug antibody levels is ≤5% (1 in 20); while for a risk of 2% (1 in 50) 150 are required to be studied, and 300 for risks of 1%. A lack of comparable immunogenicity assessment prevents ICBs from being used in switching brands mid-treatment.

Step 8: Comparative clinical studies: safety and efficacy. European and US regulators emphasize that pharmacological rather than purely clinical endpoints may be the most sensitive assessment of any significant clinical difference. However, some effects, such as cardiac toxicity induced by trastuzumab, require suitably powered clinical studies with several years of patient follow-up for accurate assessment. The WHO reminds drug regulators that if a comparative trial cannot show differences between a follow-on biologic and a reference biologic, it may be due to poor assay sensitivity or underpowered or deficient statistical design.[40]

In some countries with less stringent regulation, copies of biologics have been marketed without clinical trials,[42] or based on studies that were limited in scope, size, or scientific rigor.[43] A lack of clinical comparability studies in the most sensitive setting means that "residual uncertainty" is higher. In the first instance, ICBs have been found to receive approval before the completion of comparative studies, as was the case for a rituximab ICB that was approved in Argentina.[44] Examples of limited studies include a filgrastim ISB assessed using a phase IV study of 29 patients, of whom five were lost to follow-up. No comparative efficacy or safety data were shown, and no immunogenicity was assessed.[45] In another example, a rituximab ICB was approved based on a 70-patient PD study for CLL. In this study, the non-inferiority margin was –20%, meaning that the ICB could be 6.8% worse than placebo and still not be inferior.[41] In

comparison, far larger efficacy and safety trials have been required for rituximab biosimilars approved in Europe.

Step 9: Phase IV post-marketing surveillance and pharmacovigilance. Not all side effects can be predicted from the mode of action of a drug. Pharmacovigilance, periodic safety update reporting (PSUR), and reporting any manufacturing process changes are lifelong requirements of all Market Authorization Holders. There may be subtle differences between the reference biologic and biosimilars from different manufacturers – and from all manufacturers over time – such that adverse event reporting needs to be specific to brand and batch. The WHO requires that a pharmacovigilance plan be submitted at the time of submission of the application and should be functioning at the time of approval; however, most ICBs are developed and used in countries with less than ideal pharmacovigilance.[40]

For example, in Europe, PSUR is required monthly for 2 years, then annually for the following 2 years, and thereafter every 3 years; while in India, a formal national pharmacovigilance program only started in January 2005 and is based on half-yearly PSUR for 2 years and after that yearly for another 2 years. After that period, only spontaneous reporting will discover problems.[46] The reliability of this vigilance is low, for India has significant underreporting of adverse events from all stakeholders, with a far lower chance of detecting events.[47] Problems of pharmacovigilance in India are made more difficult by misunderstandings of the term 'biosimilar'.[48] Distribution services for biologics also matter – since many biologics need a refrigerated cold chain to avoid dangerous degradation. Post-approval samples from illegally imported epoetin ICBs in Thailand have been shown to contain aggregate levels exceeding the specification of <2% in samples seized from smugglers and retail pharmacies, indicating the likely entry of smuggled biologics into circulation.[49]

Key points – intended copy biologics: what are they and does it matter?

- Biosimilars are assessed using stringent comparability assessments to demonstrate a clinical equivalence to the reference biologic without compromising efficacy and safety.
- ICBs are follow-on biologics that have not been developed to biosimilar standards of the WHO.
- ICBs are mainly found in LMICs where regulations concerning biosimilars have either only recently been established or do not meet WHO standards.
- By definition, an ICB misses out or underpowers one or more steps of the biosimilar regulatory pathway.

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Pharmacology

6 Impact of intended copy biologics on medicines use

HEALTHCARE

Biologics are increasingly listed on the WHO Model List of Essential Medicines. However, the high costs associated with these medicines make access unaffordable to people in low- and middle-income countries (LMICs). Therefore, manufacturing affordable biosimilars is critical in expanding access to these medicines in LMICs.[1] As discussed in the previous chapter, LMIC regulations pertaining to biosimilars have either only recently been established or do not meet WHO standards. This has allowed intended copy biologics (ICBs) to enter these markets, often in the presence of both the reference biologic and its biosimilars.[2,3]

ICBs – problems with quality. Since ICBs are defined as having missed out or underpowered one or more steps of the biosimilar regulatory pathway, issues around quality will invariably arise. This underscores the importance of comprehensive pharmacovigilance during post-marketing surveillance to rapidly identify and respond to clinical issues when they arise.

Some adverse events can only be identified during post-marketing pharmacovigilance, given the very low incidence of occurrence. One such severe event is pure red cell aplasia (PRCA), known to be triggered by some erythropoietin products. Epoetin ICBs produced in Thailand have been reported to be associated with a significant rate of severe toxicity through anti-drug antibody-driven PRCA that was only detected by pharmacovigilance 9 years after introduction. This incident led to the formation of the national immunogenicity surveillance registry of erythropoiesis-stimulating agents with subcutaneous exposure.[4]

Given the issues experienced with ICBs, the fact that these are often marketed in LMICs alongside reference biologics and biosimilars under regulations that fail to clearly distinguish between the products has caused particular confusion, especially between ICBs and biosimilars. ICBs are also a tempting option for healthcare providers as they are often substantially lower in price compared to biosimilars.[5]

Confusion between biosimilars and ICBs. Distinguishing between biosimilars and ICBs has been hampered for several reasons. First, as regulations have been developed and updated, so has the

nomenclature. Even among countries with robust biosimilar approval processes, the nomenclature has only recently been standardized, and the term biosimilar was initially not used among all these countries (Table 6.1).[6] In LMICs, ICBs were often approved as biosimilars before regulations concerning biosimilars approval were established. In such cases, products on the market that were correctly labeled as biosimilars based on old regulations now do not necessarily meet the newer stringent requirements for biosimilars. In one instance, Solumarv, an insulin follow-on biologic, was refused authorization as a biosimilar by the European Medicines Agency (EMA) after being found to be not comparable with the reference biologic. However, this product is now available in India, Russia, South Africa, and Tanzania using the brand name Biosulin®.[2]

The second issue is mislabeling, whereby companies deliberately claim that an ICB is a biosimilar but do not have the data to support these claims.[7] Thirdly, LMIC healthcare professionals and patients, already unfamiliar with biosimilars, are less likely to understand how to distinguish between ICBs and biosimilars even when the former in no way claims to be a biosimilar. An online survey of 399 physicians from Latin America found that 51% of respondents could not distinguish between ICBs, reference biologics and biosimilars.[8]

The difficulties of telling ICBs and biosimilars apart create doubt in healthcare professionals and patients about the safety of biosimilars, especially when ICBs make news headlines due to safety concerns.[6] Furthermore, such confusion places doubt on the biosimilar approval pathway. If comparability data on ICBs cannot be relied upon, there will be an expectation that both ICBs and biosimilars require suitably sized clinical trials to demonstrate safety and efficacy.[9]

The consequence of a lack of trust in the safety of biosimilars due to the presence of ICBs in LMICs is a lack of uptake in these countries which need them the most. As a result of limited uptake, prices remain beyond the reach of most people residing in LMICs, restricting accessibility. There has, however, been progress in countries adopting WHO guidelines for biosimilars, leading to a greater convergence of regulations.[6] In addition, steps are being taken to address legacy ICBs and strengthen and promote biosimilar approval pathways, as will be discussed in the next chapter.

TABLE 6.1

Convergence of country-specific nomenclature around biosimilars

	2010	2019*
WHO	Similar biotherapeutic products	Similar biotherapeutic products
Canada	Subsequent entry biologics	Biosimilars
China	Biosimilars unofficially† used	Biosimilars
Egypt	–	Biosimilars
EU	Similar biological medicinal products (biosimilar)	Similar biological medicinal products (biosimilar)
Ghana	–	Biosimilar products
India	Biogeneric products unoffcially† used	Similar biologics
Indonesia	–	Biosimilar products
Iran	–	Biosimilars
Japan	Follow-on biologics	Follow-on biologics (as a synonym for biosimilars: indicated on the first page of the guidelines)
Jordan	–	Biosimilars
Malaysia	Biosimilars	Biosimilars
Peru	–	Similar biological products
Republic of Korea	Biosimilars	Biosimilar products
Singapore	Similar biological (biosimilar) products	Biosimilars
Thailand	–	Biosimilars
Ukraine	–	Similar biological medicinal products (biosimilar)
USA	–	Biosimilars
Zambia	Biosimilar medicines	Biosimilars

CONTINUED

TABLE 6.1 CONTINUED

Convergence of country-specific nomenclature around biosimilars

	2010	2019*
Brazil	Biological products developed by comparability pathway (vs new biological products)	Biological products developed by comparability pathway (vs new biological products); biosimilars unofficially† used
Cuba	Known biological products (vs biological products)‡	Multi-source known biological products
Russia	–	Bioanalog (as a synonym for biosimilars: defined in the Federal Law)

*The majority of survey participants have now adopted the term 'biosimilar', 'similar biological product' and/or 'similar biotherapeutic product' and are included in the red box in the table. Participants who did not adopt one of these are shown outside the red box.
†Unofficially: not defined in the regulations or guidelines but commonly used.
‡Cuba: guidelines did not exist, but biosimilars were categorized into 'known biological products' in draft new regulation.

Key points – impact of intended copy biologics on medicines use

- In LMICs, ICBs can often be found alongside the reference biologic and its biosimilars.
- Since ICBs are defined as having missed out or under-powered one or more steps of the biosimilar regulatory pathway, issues around quality will invariably arise.
- ICBs and biosimilars are often not clearly differentiated, creating confusion and a lack of trust in the safety of biosimilars as a result.
- Such concerns limit biosimilar uptake in LCIMs, resulting in higher prices of the existing reference biologic, which restricts accessibility.

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7 Solutions to the regulatory problem and the WHO approach

HEALTHCARE

Without unified regulations on the approval of biosimilars, intended copy biologics (ICBs) have been produced in low- and middle-income countries (LMICs) in competition to reference biologics and biosimilars. These ICBs do not meet the WHO regulatory standards of biosimilars and have been associated with various clinical issues post-marketing. Healthcare professionals often cannot distinguish between ICBs and biosimilars, generating confusion and casting doubt on the biosimilar regulatory pathway. To address this, the WHO and regulatory agencies worldwide have implemented various strategies to strengthen biosimilar approval mechanisms and address legacy ICBs.

Distinguishing between ICBs and biosimilars. A 2020 WHO survey found that naming and labeling biologics/biosimilars in most countries does not follow specific guidelines.[1] To facilitate a clear distinction between ICBs and biosimilars, the WHO has recommended avoiding the terms similar biotherapeutic product (SBP) or biosimilar when naming and describing products that have not followed the biosimilar regulatory pathway.[1] The WHO recognizes that trust around biosimilars can be strengthened by clearly delineating between ICBs and biosimilars; however, this process will take time, particularly in resource-constrained LMICs.[2] In 2022, the WHO shifted away from the term SBP and adopted the term biosimilar.[2]

The concept of reliance and joint review when approving biosimilars. The lack of resources available to national regulatory authorities is a problem for many LMICs, meaning that implementing updated regulations and guidelines is often slow or unfeasible.[1] Therefore, short-term measures include some countries, particularly Africa, recognizing the approvals of other regulatory agencies conducting expert reviews and licensed biosimilars. With this approach, the government is reliant upon the decisions of an external regulatory authority for their biosimilar approvals. An adaption includes jointly reviewing a biosimilar with other regulatory authorities.[3] This approach prevents duplication of the review process in the interim, while these countries aim in the long term to develop their own guidelines in line with WHO guidelines.[4]

In addition to initiatives by the WHO, national regulatory authorities are collaborating to improve access to biosimilars. In 2020, the Access Consortium was established, incorporating regulatory agencies from Australia, Canada, Singapore, Switzerland and the United Kingdom.[4] The Access Consortium has aimed to facilitate work-sharing between authorities and to reduce duplication. More specifically, the Access Biosimilars Working Group is tasked with facilitating the exchange of regulatory evaluation information, joint assessments of marketing authorization applications and discussions on emerging regulatory issues.[5]

Pre-qualification. Another approach to fast-tracking biosimilar introduction into LMICs, thereby reducing the reliance on ICBs, is pre-qualifying biosimilars, allowing countries with limited resources to procure safe, effective, quality-assured biosimilars. Pre-qualification is based on assessing biosimilar compliance to WHO standards.[2] The WHO pre-qualification of biosimilars piloted rituximab and trastuzumab to develop these guidelines and templates, which can be applied to other biosimilars. There are two pathways to pre-qualification. The first route is via a full assessment pathway for biosimilars registered through a non-stringent regulatory authority and based on a reference product that was approved by a stringent regulatory authority. The second pathway is an abridged assessment pathway for biosimilars registered with a stringent regulatory authority and marketed in the countries of registration.

Converging biosimilar regulations. In some LMICs, regulations around follow-on biologics were developed before the availability of EU and WHO guidelines and standards. Under such rules, these ICBs were approved and entered various markets. One example is Brazil, which, before 2002, approved biologics using guidelines for small-molecule drugs. In 2002, these guidelines were updated and biologics were referred to as new or non-new products. Then, in 2010, new guidelines were adopted which introduced the term SBP, which aligned with the WHO guidelines at the time. These new guidelines, however, still allowed for non-innovative products to be licensed through a stand-alone pathway when comparability was not possible or not applicable.[3] As seen with Brazil, there has been a gradual alignment with WHO regulations.

Most countries now have some form of biosimilar regulation in place. In India, however, the regulator, the Central Drugs Standard Control Organization (CDSCO), in 2021 continued to approve follow-on biologics as Indian similar biologics (ISBs). As discussed in previous chapters, ISBs fall short of the WHO biosimilar approval standards and are, therefore, designated as ICBs. The regulations for ISBs can hamper Indian manufacturers whose standards meet those of the WHO. Examples include Biocon, who have produced a trastuzumab biosimilar, and Intas/Accord, who have produced filgrastim and pegfilgrastim biosimilars. In both these cases, these biosimilars were developed in India and received approval as biosimilars by regulators in Europe and the USA, not India.[6]

Reassessing ICBs already on the market. Concerning ICBs that were on the market before countries implemented biosimilar regulations, the WHO is encouraging these national regulatory authorities to review and assess such ICBs within the updated regulatory framework.[2] So far, several countries have begun reviewing these ICBs.

In Brazil, all ICBs licensed before 2002 have undergone reassessment. In Cuba, where medicines are required to renew their market authorization every 5 years, the national regulatory authority has introduced the WHO guidelines into this process as of 2019. Egypt has, as of 2015, implemented the WHO guidance document, and biologics that previously were not assessed as biologics are now being reviewed. Ghana, which adopted the WHO guidelines in 2013, has distinct requirements for biosimilar approval. Market authorization is renewed every 3 years based on the latest guidelines, and biosimilars that do not meet the latest criteria will not have their approval renewed. Jordan has reviewed and withdrawn several ICBs that had received authorization before 2009 when no biosimilar guidelines had been established in that country. In light of pure red cell aplasia (PRCA) that was associated with erythropoietin products, Thailand reviewed all of these products in 2013 and revoked authorization for several ICBs when license holders were unable to supply the requested data. Notably, some countries have not yet implemented WHO guidelines; as at 2021, these countries included China, Singapore and Ukraine.[1]

Key points – solutions to the regulatory problem and the WHO approach

- The WHO and regulatory agencies worldwide have implemented various strategies to strengthen biosimilar approval mechanisms and address legacy ICBs.
- WHO recommends avoiding the terms SBP or biosimilar when naming and describing products that have not followed the biosimilar regulatory pathway.
- Resource-constrained countries can, in the short-term, rely upon the decisions of an external regulatory authority for their biosimilar approvals
- The WHO has successfully piloted pre-qualifying biosimilars based on assessing compliance with WHO standards, which can then be readily available for LMICs.
- Most countries now have some form of biosimilar regulation in place.
- WHO is encouraging national regulatory authorities to review and assess existing ICBs based on WHO guidelines.

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Pharmacology

8 Practical steps when quality is uncertain

HEALTHCARE

As of July 2024, there were 88 authorized biosimilars listed on the European Medicines Agency (EMA) Medicines page. This number is expected to rise considerably as more reference biologics lose patent protection. Deciding on what constitutes the best value when choosing a reference biologic or biosimilar for a hospital therapeutic formulary is complex and includes many factors beyond price.[1]

Differentiating between the reference biologic, biosimilars and ICBs. When meeting to identify the best value biological drug, purchasers should understand how biosimilars are developed and approved and the regulatory pathways associated with biosimilars. Furthermore, a clear understanding of the differences between the reference biologic, biosimilars and intended copy biologics (ICBs) is required. To assist purchasers, they should use reliable scientific/regulatory documents such as European public assessment reports and US prescribing information.[1]

Selecting the best value biologic. Choosing the best biologic or biosimilar is no longer an either-or decision, given that reference biologics often now have more than one biosimilar. With increased competition, manufacturers increasingly introduce value adds to their products, further complicating identifying the best value product. Thus, purchasers often struggle when identifying criteria over and above the price that can be used to choose between the reference biologic or biosimilars.[1]

Criteria that can be used during selection. Criteria that influence the best value can be divided into three categories, namely: product-, service- and patient-driven criteria (Table 8.1). The inclusion of such criteria during selection is dependent on the product context. Previously, evaluating biosimilar safety and efficacy was suggested in part to determine best value; however, this is now considered redundant because of the robust EU and US regulatory frameworks that are used to evaluate biosimilars together with more than 15 years of real-world data demonstrating safety and efficacy.

Weighting criteria and choosing the best value biologic. When deciding how to weight criteria, it is crucial to consider the relative importance of each. The criteria weights should be discussed as these depend on the country and healthcare institution. Importantly, each

TABLE 8.1

Criteria that can be considered when identifying a best value biological product[1]

Product-driven criteria	
Technical product features	Available strengths
	Product administration form: available administration routes, efficient product use, …
	Storage conditions: stability, shelf life, …
	Reconstitution: handling needs, time, …
	Packaging: lookalike, box volume, ease of handling, …
Indications	Authorized indications
	Reimbursement of indications
Real-world experience	Data to substantiate claims regarding patient experience, injection pain, …
Service-driven criteria	
Supply conditions	Number and location of manufacturing, packaging and storage sites
	Logistics arrangements
	Modalities for urgent deliveries
	Customer support
	Policy on returns/expired products
	Policy on strategic stocks
Value-added services	Therapeutic drug monitoring
	Training and educational support for healthcare professionals
Environment and sustainability	Sustainability/environmental company policy (production, transport)
	Sustainability/environmental policy of subcontractors
	Packaging material

CONTINUED

TABLE 8.1 CONTINUED

Criteria that can be considered when identifying a best value biological product[1]

Patient-driven criteria	
Product user-friendliness	Ease of use of device Injection comfort
Patient support programs	Online disease education, device training, adherence program, patient informational material, nurse service at home, …

criterion should be weighted sufficiently to affect decision-making beyond price. Selecting criteria and assigning weights must be a transparent and evidence-based process. Before meeting to determine the best value biologic, objectively measurable questions must be formulated based on the chosen criteria, and the scoring of answers needs to be agreed upon.[1]

Understanding why prices may vary. Price savings of biologics can vary for two reasons. The first is visible savings in list prices, primarily spurred by market competition by introducing biosimilars (Figure 8.1). The second reason is confidential rebates. Rebates can offer substantial savings; however, in the long run, they can hamper competition. Confidential rebates impact the effective market price that competitors must determine to compete. Given the lack of transparency around rebates, the effective market price can be challenging to ascertain, hampering market entry.[2]

Rebate traps and walls. Manufacturers use rebates to encourage purchasers to include their biologics in formularies. Rebates can be conditional on volume or performance and can provide a discount on the list price of a single product or combination of products. Furthermore, rebates are often introduced following the introduction of biosimilars.

Rebates can be procompetitive in the presence of multiple competitors; however, there are several negative consequences. Patients often do not directly benefit from rebates; therefore, their

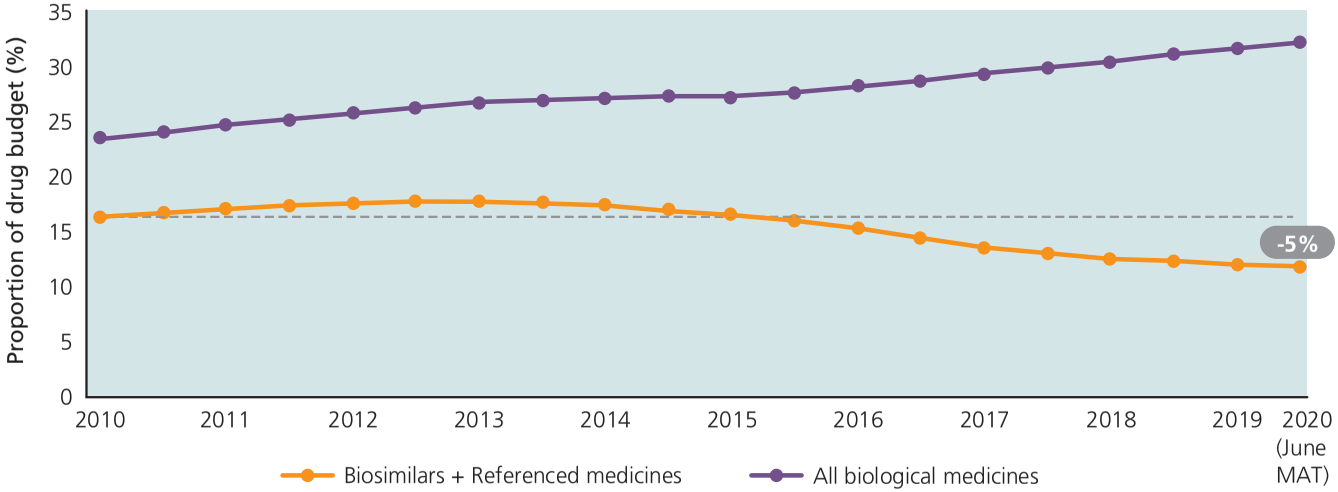

Figure 8.1 The impact of biosimilars on visible savings.[2]
Note: Biologic accessible market includes referenced medicines, non-referenced medicines, and biosimilar molecule sales at list price (excluding rebates and discounts) in local currency Euros between 2010 and 2020.
Source: IQVIA MIDAS® June MAT 2020 (Rx only).

out-of-pocket expenses are higher. Rebates can also increase the listing price, and it has been demonstrated that rebate growth is linked to increased list prices that do not correspond with an increase in the net price.

Rebate walls are anti-competitive practices often affecting biological products that favor the reference biologic over a lower-cost biosimilar. A rebate wall involves manufacturers leveraging their market share by maintaining rebates to purchasers on the condition that they exclusively purchase or favor their product over competing drugs. Purchasers are then incentivized to buy the more expensive reference biologic based on exclusivity or volume to maintain their rebates even though a biosimilar can be purchased at a lower per-unit price. There are three types of rebate wall.

The first is a basic single product, single indication rebate wall. In this situation, the reference biologic has the entire market share. Should a purchaser wish to include a biosimilar in their formulary, they would be penalized by the reference manufacturer if a threshold volume is not maintained. The purchaser is then stuck in a rebate trap as the loss of rebates through introducing the biosimilar exceeds the gains made in using the lower-cost biosimilar.

The second type of rebate wall is a single product with multiple indications. In this scenario, the combined volume of sales of the reference biologic for all its indications exceeds the volume of biosimilar sales that may not have specific indications due to regulatory exclusivity or patents. As in the first rebate wall type, the gains made in using the lower-cost biosimilar cannot cover the rebate loss from the combined reference biologic indications.

The most challenging type of rebate wall is where the manufacturer threatens to withhold rebates on a bundle of products if the purchaser opts to introduce a biosimilar. Biosimilar manufacturers often cannot offer the other products in the bundle and are, therefore, at a significant disadvantage.[3]

Rebate traps are often linked to a lack of confidence in biosimilars as this means limited uptake and, therefore, insufficient volumes in sales of biosimilars to overcome the rebate wall. The gains in short-term rebates disincentivize purchasers from opting for biosimilars that provide long-term benefits, which has the knock-on effect of

harming competition and innovation. Therefore, a multipronged approach is needed to address these issues to reduce perception-related barriers and introduce policies that discourage anti-competitive strategies.[3]

Key points – practical steps when quality is uncertain

- Purchasers should understand how biosimilars are developed and approved using the associated regulatory pathways.
- Purchasers should clearly understand the differences between the reference biologic, biosimilars and ICBs.
- Selecting the best value biologic goes beyond price and includes product-, service- and patient-driven criteria.
- Incorporating criteria into the decision-making process should be transparent and evidence based.
- Biologic prices can vary due to visible savings and confidential rebates.
- Rebate walls involve manufacturers leveraging their market share by maintaining rebates to purchasers on the condition that they exclusively purchase or favor their product over competing drugs.

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Pharmacology

9 Biosimilars globally in endocrinology, renal medicine, hematology, oncology, and immunology

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Biosimilars in endocrinology and diabetes

Background. The incidence of type-1 diabetes and type-2 diabetes continues to rise globally, with low- and middle-income countries (LMICs) accounting for 79% of people with diabetes. The increase in the incidence of diabetes has fueled the demand for insulin, increasing costs and restricting access. These costs have forced 1 in 4 people with diabetes in the USA to ration their insulin dose.[1] Furthermore, only 55–80% of facilities dispensing medication in LMICs have access to insulin. Therefore, reducing the cost of insulin is crucial to support and expand access to this essential medication.[2]

The demand for regular human insulin is expected to grow; however, as of 2022, only three manufacturers controlled 99% of the market in value and 96% in volume. Therefore, increasing supply by the manufacturing sector may reduce costs – estimates suggest the annual cost of insulin analog treatment in the USA could be reduced by over 50-fold.[3] Biosimilars can be utilized to increase competition in this market, given the opportunity created by the expiry of first-generation insulin patents.[4]

Devices to self-administer insulin. An important distinguishing feature of insulin biosimilars is that the insulin is self-administered; furthermore, dosing depends on blood glucose level, which varies throughout the day. Given this feature, the device used to administer insulin is crucial for ensuring adherence, effectiveness, and safety.[5] The device or delivery system can differ between biosimilars and the reference biologic; therefore, on switching, patients and healthcare practitioners need to be aware of how the newer device is used, and training may be required.[1] Changes in devices may represent a greater concern to the patient than the switch to a biosimilar.[3] That said, no device-related challenges have been reported in post-marketing safety surveillance, and changing to a biosimilar with a different device can be done and does not increase adverse effects.[1]

Underuse of biosimilar insulin. In some countries, the uptake of available biosimilar insulin has been slow. In the UK, there have been greater concerns over the safety and efficacy of biosimilars among diabetologists compared to clinicians in other

specialties. This slow uptake is also apparent in the proportion of prescribed insulin glargine biosimilars, which comprise only 9% of total prescriptions compared to 62% for biosimilar therapies in gastroenterology. A further study has estimated that a complete switch to biosimilar insulin glargine would have generated £25.6 million in savings; however, in practice, only £900 000 in savings were achieved without a complete switch. Such underuse of biosimilars in diabetes highlights the importance of creating awareness among clinicians.

Underuse of insulin biosimilars has also been reported in Brazil for reasons similar to those in the UK, such as mistrust. Furthermore, the development of biosimilar policy by Brazil's healthcare system has lagged behind the introduction of biosimilars. Toward the end of 2023, the Brazilian Health Regulatory Agency (ANVISA) enacted new legislation that streamlined regulatory requirements for biosimilars, putting them in line with international guidelines to expand the supply of biosimilars. The changes introduced greater flexibility and reduced the scope of studies required for comparability, making it easier for biosimilars to be approved.[6]

Real-world experience with biosimilars: Canada

Biologics accounted for 27.3% of drug spending in Canada in 2018 while only making up 1.5% of the prescription volume. Furthermore, the prices of biologics were second only to those of the USA when compared to those of the Organisation for Economic Co-operation and Development (OECD) countries. Spending on these drugs has increased three-fold in the past decade and is projected to grow steadily. Therefore, there has been a concerted effort to maximize cost savings.[7]

Currently, 1000 biologics are marketed in Canada, yet only 56 biosimilars have been approved as of 2024.[8] The first biosimilar for insulin glargine was approved in Canada in 2015 and endorsed by the Common Drug Review. In 2017, this biosimilar was incorporated into all provincial formularies; however, switching was only introduced provincially in 2019. Furthermore, policies are in place in certain provinces to replace the reference biologic with the biosimilar. British Columbia and Alberta were the first to begin replacement in 2020. New start policies have also been adopted in provinces and by insurers.[7]

In 2023, there were five insulin biosimilars approved for use in Canada: insulin glargine (2), insulin lispro (1) and insulin aspart (2).[9]

As a result of differences in approaches provincially, the uptake of biosimilar insulin glargine has varied significantly. In 2020, the proportion of biosimilar insulin glargine prescribed nationally was around 60%. This figure was above 90% for British Columbia, followed by Prince Edward Island, New Brunswick and Nova Scotia at above 80%. Alberta and Quebec were below the national average at above 50%. In contrast, the lowest uptake was seen in Manitoba, Ontario, and Saskatchewan, with an average of 20%. These provinces only had a new start policy in place at the time. The success of adoption seen in British Columbia resulted from the switching policy introduced in 2019.

The differences between provinces also provide evidence to suggest that simply incorporating biosimilars into the provincial formularies does not guarantee uptake. When biosimilar insulin glargine was incorporated into the provincial formularies, New Brunswick, Nova Scotia, and Prince Edward Island also introduced special authorization for the use of the reference biologic. Uptake climbed rapidly on the induction of this requirement before reaching above 80% in all three provinces. In the provinces of Ontario and Saskatchewan, where no such authorization was required, the uptake of biosimilar insulin glargine remained below 30% in 2020.[7] To address this lag in uptake, in 2023, patients in Ontario who make use of the Ontario Drug Benefit were required to transition to biosimilar insulins by the end of that year.[10] The introduction of this policy is expected to save approximately CA$ 160 million.[9]

Indication extrapolation has been identified as one of the reasons behind the observed clinician and patient hesitancy to use biosimilars. The low overall uptake of biosimilars in Canada can dissuade manufacturers of biosimilars from entering the market, which further exacerbates access and cost. Several mechanisms have been put forward to promote uptake.[7]

- Policy harmonization between provinces is to be encouraged. The effects on uptake due to policy differences are evident. Provinces have been encouraged to align their policies to achieve maximum uptake based on the existing data.

- More needs to be done to educate patients and clinicians on the safety and effectiveness of biosimilars, as has been elaborated in previous chapters.
- Manufacturers should be encouraged to consider value-added services in addition to direct costs when entering the market, as these services contribute to the overall value of biological therapies.[7]

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Introducing biosimilars in renal medicine

Background. An estimated 850 million people have chronic kidney disease (CKD) globally.[1] In patients with CKD, kidney damage often affects the secretion of erythropoietin (EPO), placing these patients at risk of developing anemia.[2] In the USA, patients with CKD are twice as likely (15.4%) to have anemia than the general population (7.6%). At stage 5 end-stage CKD, the prevalence of anemia increases to 53.4%. Patients with CKD-related anemia are at greater risk of further adverse health outcomes.[1]

Fortunately, recombinant human EPO (rhEPO) treatment can partially correct the anemia and substantially increase the quality of life of patients with CKD.[3] However, given the demand caused by CKD-related anemia, there is insufficient supply, and the cost of treatment has risen. The annual cost of rhEPO is between US$ 24000 and US$ 28000, depending on hemoglobin levels. In perspective, in 2019, the world average for gross domestic product (GDP) per capita stood at US$ 11570, putting the rhEPO treatment far beyond most patients with CKD.[1]

In 2007, HX575 was the first epoetin alfa biosimilar to be approved in Europe. The 15 years of clinical experience using HX575 have identified no new risks or safety concerns.[3] Thus far, three biosimilars have been approved for epoetin alfa in Australia, Canada, Europe, Japan and the USA. Furthermore, there have also been 38 follow-on biologics that have not been approved in the above-listed regions but are approved elsewhere.[2]

Anti-recombinant human epoetin-induced pure red cell aplasia in Thailand. A severe complication that can arise from rhEPO treatment is anti-rhEPO-induced pure red cell aplasia (PRCA). rhEPO-induced antibodies neutralize both rhEPO and endogenous EPO, causing EPO serum levels to become undetectable, further exacerbating anemia. In such cases, a blood transfusion is required to relieve symptoms.[4]

Genetics plays a role in rhEPO immunogenicity based on variations seen in the human leukocyte antigen (HLA). Furthermore, PRCA incidence has also been linked to rhEPO product quality. The immunogenic stabilizer polysorbate-80, used in the reference epoetin, increased PRCA incidence and was suspected of leaching organic

compounds with adjuvant properties from uncoated stoppers. The reintroduction of coated stoppers led to no further reported PRCA cases. Furthermore, cold chain and subcutaneous administration have also been identified as factors that contributed to PRCA.[3–5]

In Thailand, the incidence of PRCA is 1.7/1000 patient-years, which is disproportionately higher compared to Western countries with an incidence of 0.07/1000 patient-years. Factors contributing to this higher incidence include higher levels of susceptible HLA genotypes in the Thai population and the numerous intended copy EPO products approved for use in Thailand based on a classic generic regulatory pathway and registered as generic products.[4,5] Analysis of intended copy rhEPO products performed in 2014 identified significant differences compared to the reference biologic, Epogen®. Differences affecting immunogenicity included high levels of protein aggregation, substantial protein fragmentation, and, in one case, endotoxin levels that exceeded US Food and Drug Administration (FDA) limits. At the time of the study, biosimilar guidelines were still under development in Thailand. This example underscores the importance of establishing biosimilar guidelines to ensure products meet the specifications of the reference biologic in terms of efficacy, quality and safety.[5]

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Biosimilars in hematology

Background. Biological treatments have transformed the management of hematological diseases; however, the high cost of these treatments has placed pressure on healthcare budgets and thus limited patient accessibility.[1] To make treatment more accessible to patients, medicines agencies have actively supported the introduction of biosimilars. In hematology, biosimilars first appeared in the early 2000s, with EPO and granulocyte colony-stimulating factor (G-CSF) biosimilars being released in Europe between 2007 and 2008.

Following on from the biosimilar growth factors, in 2017, the first biosimilar for rituximab was introduced, which has made a competition-boosting impact on the biological market and was envisaged to result in a 40–60% reduction in the overall price of the drug.[2] These cost reductions have largely come to fruition with rituximab. For example, hospitals that completely transitioned to the rituximab biosimilar in the UK saw substantial savings within the first 12 months, given that the biosimilar was priced at 55% less than the reference product.[1]

Biosimilars present an opportunity to expand treatment access for patients with hematological diseases; however, as with biosimilars in general, knowledge among healthcare workers of biosimilars in the hematological context is low, creating a barrier to access. In Nigeria, for instance, healthcare workers scored, on average, 44% for tests designed to assess their understanding of biologics and biosimilars in treating hematological malignancies. However, through introducing educational programs, this awareness can be shifted.[3]

Rituximab biosimilar adoption. The presence of rituximab biosimilars on the market has expanded patient access, especially in LMICs such as India. A study from the Tata Memorial Center in Mumbai reported that in 2010, only 35% of patients with diffuse large B-cell lymphoma could afford rituximab; a decade later, accessibility now stands at 95%, primarily credited to the introduction of biosimilars. Biosimilars have also reduced the cost of the reference biologic in India. When the reference rituximab was launched in India in 2002, the price was INR 135 000 (US$ 1849), the maximum retail price (MRP). In 2007, the first biosimilar was released and priced at INR 40 000 (US$ 550), which led to a 40% reduction in the price of the reference biologic to INR 80 000 (US$ 1100). Adding more

biosimilars, while only slightly reducing MRP has further improved patient access to rituximab.[4]

Safety concerns around intended copy rituximab. Before Mexico passed biosimilar approval regulations, the intended copy of rituximab, Kikuzubam, was approved by the Mexican Ministry of Health for treating rheumatoid arthritis.[5] Kikuzubam was manufactured and marketed in Mexico; however, no clinical data supporting the assessment of biosimilarity with the reference biologic were publicly available. Given the lack of clinical data concerning efficacy and safety and reported anaphylactic reactions, the Mexican Federal Commission for Protection Against Health Risks withdrew the intended copy from the market in 2014.[6,7]

Real-world experience of biosimilars: Saudi Arabia

The formulary adoption of biosimilars in The Kingdom of Saudi Arabia (KSA) aligns with Saudi Vision 2030. KSA is the largest biosimilar market in the Middle East and Africa (MEA), with about US$ 35 million in sales. The Saudi Arabian General Investment Authority speculated that the market for biosimilars in the country is expected to grow at a compound annual growth rate of around 12% between 2021 and 2026.[8]

Integrating biosimilars into oncology clinical practice is necessary. A KSA simulation study evaluated the cost efficiency and expanded access to care by switching from reference filgrastim and pegfilgrastim to biosimilar filgrastim in 4000 patients in the country. Savings from conversion from reference filgrastim to a biosimilar filgrastim were approximately US$3 million, enabling supportive care treatment for up to an additional 9244 patients. Similarly, with reference pegfilgrastim, savings from conversion ranged up to US$ 12 million, which enabled supportive care for an additional 32 283 patients.[8,9]

Saudi Arabia started using biosimilar filgrastim in 2014, and it has been reported that the substitution of Neupogen® has resulted in very significant cost savings when used for prophylaxis and management of febrile neutropenia in about 77% of the patients in the Ministry of National Guards Health Affairs (MNGHA). Furthermore, the substitution of rituximab is expected to have a 50–60% cost saving in different oncology hospitals of the KSA.[10]

The Saudi Food and Drug Authority (SFDA) has approved many biosimilars for monoclonal antibodies such as rituximab, trastuzumab and bevacizumab. The MNGHA was the first organization to adopt biosimilars of these three monoclonal antibodies in 2020–21 with an annual cost saving of around SAR 30 million per year. The rituximab biosimilar was implemented only partially, and mainly in in-patient regimens for treating malignant and non-malignant conditions. Subcutaneous (SC) rituximab was kept in the formulary since there is a major advantage with SC rituximab regarding ease and convenience of administration. The SFDA has approved SC rituximab in a fixed dose of 1400 mg. It is administered over 5 minutes compared with intravenous (IV) administration over more than 6 hours. With rituximab in the KSA, the emergence of second-generation SC rituximab has offset some of the benefits gained through the biosimilar rituximab. Therefore, the MNGHA decided to limit IV biosimilar rituximab use to B-cell acute lymphocytic leukemia, salvage regimens for lymphomas, chronic lymphocytic leukemia and all non-malignant conditions.[8,10]

Building trust in biosimilars is a vital component in this paradigm shift. Real-world clinical data will be an important next step in instilling trust in healthcare providers. King Abdulaziz Medical City Jeddah (KAMC-J) is currently doing many real-world evidence studies in extrapolated indications on the use of oncology biosimilars and preliminary unpublished data are reassuring regarding the comparability of efficacy and safety of oncology biosimilars.[8]

The KAMC-J recently published the first real-world evidence study from the Middle East on biosimilar filgrastim to mobilize and collect stem cells. This retrospective study compared biosimilar filgrastim with the reference filgrastim for peripheral blood stem cell mobilization, collection of CD34+ stem cells, and engraftment in patients undergoing autologous and allogeneic stem cell transplantation. The study showed that there was no difference between Zarzio® and Neupogen® in the amount of $CD34^+$ stem cells collected at leukapheresis and hence has comparable efficacy to the original G-CSF (Neupogen®) when used for mobilization in both autologous and allogeneic stem cell transplantation and was associated with significant cost saving. These results have led centers in the Middle East and elsewhere to adopt biosimilar filgrastim to mobilize and harvest stem cells.[11]

Infusion-related reactions (IRR) are possible after rituximab delivery and can be life-threatening; thus, it is recommended to give the patient one full IV dose before transitioning to the SC formulation. At the KAMC-J, an initial IV rituximab biosimilar is used, and if no severe IRR are reported, subsequent cycles are given using SC rituximab per institutional guidelines. There is currently no safety data available for this switch; however, many centers in the UK and Canada have already adopted this practice. The KAMC-J has been the first institution to retrospectively evaluate the safety of this practice and to design and complete a real-world evidence study on this practice for B-cell lymphoma. Results of this study demonstrated that only 1 of 34 patients developed IRR; however, it was grade 1 as per Common Terminology Criteria for Adverse Events v5.0, and the patient was able to complete the IV rituximab infusion in the first cycle. This study provides the first evidence that the transition from IV rituximab biosimilar to SC rituximab (MabThera) is a well tolerated and safe practice and is recommended to be implemented in other institutions (unpublished study presented in 3rd Saudi Society of Clinical Pharmacy Conference held on September 1–3, 2023).

Healthcare organizations will need to provide a structured process for integrating biosimilars into the formulary. A group at the MNGHA recently published guidance on the formulary evaluation process for biosimilars. Using the holistic approach outlined in their paper, other organizations can ensure biosimilars are thoroughly evaluated before formulary addition and key considerations are not overlooked. Further awareness of biosimilar use among healthcare workers and patients is needed. Key stakeholders such as physicians and pharmacists should be engaged in this campaign as educators. In 2021, the KAMC-J ran a successful awareness campaign for oncology biosimilars, resulting in a positive impact on the utility of oncology biosimilars. The Saudi Oncology Pharmacy Assembly, in collaboration with the Saudi Society of Oncology, has also taken on awareness at the country level, leading to an increase in the adoption of oncology biosimilars at the national level.[8,12]

The MNGHA has a unique naming strategy for biosimilars. It has recommended that the brand names be included in the computerized prescribing order entry in the Health Information System in addition to the international non-proprietary name (INN) of the drug to allow

tracking for pharmacovigilance monitoring. The biosimilar product is identified as a 'biosimilar' on the order entry screen by adding the term (Biosimilar) to the product's name e.g. Rituximab (Truxima-Biosimilar).[12]

Future directions, recommendations and opportunities. Further awareness campaigns pertaining to oncology biosimilars education among healthcare workers in the KSA and the Middle East are recommended. These campaigns need to address practical issues of extrapolation and switchability of the biosimilars to improve how they are perceived and to build the trust of healthcare providers. There is also a need to encourage real-world studies using biosimilars especially in the extrapolated indications in order to further improve the perception of biosimilars among healthcare workers.

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Biosimilars in oncology

Background. Cancer is listed as one of the top ten global causes of mortality and features more prominently in developed countries where lifestyle and an aging population lead to greater incidences.[1] Since the first biosimilar, filgrastim, was introduced in 2015, biosimilars have expanded global patient access to cancer therapy by 44%.[2] Despite this impressive expansion and incentives, barriers to biosimilar acceptance continue:

- Awareness around the availability of biosimilars is low, with only 21% of general practitioners and slightly more (26%) oncologists familiar with biosimilars.
- Switching from biologics to biosimilars is also a major concern for patients and healthcare professionals.[2]
- Concerns around biosimilar immunogenicity and how this impacts efficacy.

Biosimilar awareness and perception. A survey conducted among 1201 US physicians identified several knowledge gaps related to biosimilars, which included a lack of awareness around biologics and biosimilars, the process by which biosimilars are approved, safety and immunogenicity, and switching between the original biologic as well as between biosimilars. Furthermore, a survey of 500 US hematologists and oncologists found that 81% are hesitant to prescribe biosimilars until an average sales price has been established.[3] This demonstrates a clear need for greater awareness of biosimilars in oncology.

A model example of biosimilar awareness and adoption in oncology has been in Denmark, where uptake of a trastuzumab biosimilar reached 90% 3 months after entry into the market. This dramatic switch was accredited to Denmark's automated substitution system and close coordination between drug suppliers, administrators, clinicians and patient organizations.[4] Therefore, ensuring multistakeholder consensus is crucial to creating awareness of biosimilars.

Real-world experience with biosimilars: Latin America

In Latin America, with the exceptions of Mexico, Argentina, and Brazil, where regulatory guidelines, production, and development processes are more established, many countries face difficulties

accessing biosimilars due to regulatory, legislative, and market-related challenges. The Americas Health Foundation has convened a panel of experts in clinical oncology and health economics to deliberate on matters concerning the regulation of biosimilars. They have produced a document that elucidates the most pertinent aspects related to obstacles in accessing these biological therapies in the Latin American region and proposes recommendations and intervention strategies.[5]

Recommendations to expand access to biosimilars in Latin America

Adapt to international standards. Regulatory pathways for biosimilars should be updated according to international standards based on the recommendations provided by the WHO or the processes already implemented by the US FDA or the European Medicines Agency (EMA). Biosimilars do not require local completion of extensive Phase III and Phase IV clinical studies and can be approved based on non-inferiority evidence alone. However, expanding the role of pharmacokinetic and analytical studies of these compounds is crucial. To ensure that a biosimilar coming onto the market has the same clinical safety and efficacy as the original product, regulatory agencies need to establish well-designed pathways to achieve approval.

Standardize regulatory pathways throughout the region. Strategies should be implemented to harmonize biosimilar regulations by leveraging the initiatives already in place. The strategies include establishing a regional position through a space for regulatory convergence, where different drafts of WHO guidelines are disseminated and discussed; training and experience exchange between different local regulators; and regional cooperation in terms of cost, processes expediency, and accuracy of approvals.

Extrapolation of approvals from agencies such as the EMA or US FDA should be considered by Latin American regulatory authorities when no substantial clinical differences between the biosimilars and the original compounds are found, and biosimilarity is established. Extrapolation reduces or eliminates the need for repeating local and indication-specific clinical studies that have established the safety and efficacy of the originator product.

Separate pathways for biosimilars. A specific pathway should be implemented for biosimilars that is different from the approval pathways for generic drugs and biologic originators.

Invest in training and expanding human resources. Investment in educational programs for regulatory personnel is needed. Because biosimilar approval requires specific regulations, people in charge of reviewing applications must be specifically trained for this purpose. Establishing regional working groups to assist national regulatory authorities in biosimilar approval could be useful.

Naming. Implementing a naming convention to clearly identify and differentiate between biosimilars and originators is important.

Implementation and adherence. Once implemented, adherence to these regulations is of upmost importance. Adequate implementation of biosimilar regulations requires concerted efforts by all stakeholders to overcome organizational, normative, and information technology challenges.

Regulatory agencies. Two regulatory agencies operate in the health sector in Brazil: the Brazilian Health Regulatory Agency (ANVISA) and the National Agency of Supplementary Health (ANS). ANVISA is responsible for the sanitary control of goods subject to health regulation, including pharmaceuticals, and ANS is responsible for regulating private companies offering health insurance in Brazil.

Brazilian regulations for the approval of biosimilars were discussed and enacted by ANVISA in 2010 – Collegiate Board Resolution (RDC) No.55. The RDC has established that registration of a biopharmaceutical product may follow the pathway of an innovative drug or biosimilar. For the biosimilarity pathway, extensive preclinical documentation on the biosimilar characteristics compared to the reference product is provided, and the biosimilar must crucially demonstrate similarity to the reference product in terms of safety and efficacy based on clinical data. It is important to note that the clinical trial must be a comparative study with the reference medicine, and the outcome measures may range from drug outcomes (response rates or clinical benefit rates) to survival outcomes. In Brazil, the package insert of a biosimilar product includes information about the reference product and, in some cases, may be the same as the one provided with the reference product. Data from comparative studies

may be included in the biosimilar package insert. In addition, a biosimilar package insert includes basic information on biosimilars.

The Brazilian Society of Clinical Oncology (SBOC) actively participated in the discussion about the development and use of biosimilars in the country and acknowledged the need to share its recommendations and educate oncologists and other healthcare practitioners in clinical practice, addressing a range of issues on biosimilar development and application in Brazil.[6] Several issues were detailed, such as extrapolation and interchangeability.

Extrapolation. SBOC stated that extrapolation for each proposed indication should ideally be supported by scientific evidence from a randomized Phase III clinical trial. However, SBOC acknowledged that such studies are not always feasible and practical and may increase the costs and lengthen the approval process for new indications. SBOC also recognized that the extrapolation of indications has positive and negative arguments that should be weighed carefully by the regulatory authority. Arguments supporting extrapolation include the biological similarity between diseases, drugs that share the same therapeutic target testing in susceptible populations, and indications of the reference drug. Conversely, differences in immunogenicity, activation of biological pathways other than those associated with the reference medicine, and likely adverse effects of combination therapies are some arguments against automatic extrapolation. Thus, SBOC recommended that decisions regarding extrapolation should be made on a case-by-case basis.

Interchangeability of biosimilars is another topic still under discussion in Brazil. ANVISA allows interchangeability when the biosimilarity of a biosimilar with its reference product has been established based on clinical data from studies that aimed to show the interchangeability between the drugs. Patient follow-up and physician assessment are critical in determining whether a biosimilar can be considered interchangeable with the respective reference product. SBOC recognizes the key role of pharmacovigilance and warns of the importance of implementing a tracking system for biopharmaceutical and biosimilar products. In addition, SBOC recognizes that current pharmacovigilance programs in Brazil are insufficient and believes that cancer treatment centers nationwide should adopt more stringent pharmacovigilance practices.

Biosimilars in breast and colorectal cancer. Breast and colorectal cancer are, respectively, the second and third most common tumor types and the leading causes of cancer-related deaths in the Latin American region. Standard treatments for both cancers involve the use of biologics, such as bevacizumab (anti-angiogenic) in the case of colorectal tumors, and trastuzumab (anti-HER2 monoclonal antibody) for the treatment of HER2-positive breast cancer, which makes up around 20% of all breast cancer cases in Brazil. Trastuzumab has been the basis of this treatment in conjugate and dual blockade therapies and was approved by ANVISA in 2019. However, cost and low availability create significant barriers to accessing these drugs. There is consensus that the main advantages of biosimilars include their lower prices compared with the reference drug.[7,8] and thus biosimilars contribute to expand access to oncology treatments, providing new and advanced technologies for therapies.

Both the acceptance and adoption of biosimilars still face many challenges. Previous survey findings have demonstrated prescribers' concerns and doubts about the biosimilar approval process, the definition of interchangeability or switching and their rules, requirements for extrapolation, and safety and efficacy.[9,10] While Brazilian oncologists demonstrate a high level of knowledge of biosimilars and encouraging levels of prescriber use, extrapolation and switching treatment regimens are barriers to the effective use of biosimilars in cancer treatment.

A survey was developed using an online platform that sought information regarding responders' characteristics and use of biosimilars in Brazil.[11,12] The survey sought to investigate knowledge of biosimilars, trastuzumab biosimilars, level of comfort with extrapolation and switching treatment regimens, and opinions concerning the cost of HER2-positive breast cancer therapy. In total, 95% of respondents could identify the most appropriate definition of biosimilars and 96% felt comfortable prescribing trastuzumab biosimilars. Although 63% of respondents reported they would use a biosimilar in all settings where the reference biologic was approved, only 35% indicated they would use the biosimilar for cases involving metastatic disease. A total of 82% of oncologists favored switching

from a reference biologic to a biosimilar, while 18% indicated that they would avoid switching regimens. The major concern was the lack of studies detailing switching to other regimens and the correct timing to switch.

Encouraging biosimilar use. The Brazilian government has taken several steps to encourage biosimilar use, including urging doctors to prescribe them instead of reference biologics and fostering the growth of a biosimilar sector.[12] Brazil, like many other countries, realizes the need for more cost-effective biologics and public-private partnerships, known as productive development partnerships, to encourage the growth of the biotechnology industry and protect the country and the region from supply shortages. In order to transfer the technology to public laboratories until they gain independence to produce the biosimilar, the government guarantees the purchase of the item produced internally during the entire technology transfer period, currently set at a maximum of 5 years. To ensure the quality of national production, investments were made in research and professional training, while Brazil has also had experience producing vaccines and medicines such as rituximab through partnerships with international laboratories.

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Biosimilars in immunology

Background. Autoimmune diseases are a family of complex chronic illnesses characterized by adaptive and innate immune system dysregulation. Examples include rheumatoid disease, psoriasis and psoriatic arthritis, ankylosing spondylitis, ulcerative colitis and Crohn's disease. Most follow a chronic course, and there is overlap in many of the symptoms of each disease as well as the potential for affecting multiple organs and tissues. Several have a shared genetic background, and their development involves overlapping molecular pathways that can be activated by environmental triggers.[1]

Due to their chronic course, often incurable nature, severity of symptoms, impact on quality of life, economic productivity and mortality, many autoimmune diseases are managed intensively. Before biologics, treatment often involved symptomatic treatment; however, clinical studies show that remission of symptoms is more likely when treatment begins early with medications known as disease-modifying anti-inflammatory drugs. First-generation synthetic small-molecule disease-modifying drugs include methotrexate, hydroxychloroquine and sulfasalazine. Later development of biologic response modifiers proved to increase significantly rates of response and remission and include inhibitors of tumor necrosis factor alfa (TNFα), the "master regulator" of the inflammatory (immune) response in many organ systems. Inhibitors of TNFα include infliximab, etanercept and adalimumab, first approved in 1998, 1998, and 2002, respectively. Rituximab, a monoclonal antibody directed against the CD-20 marker on activated B cells, was first approved for autoimmune disease in 2006. By depleting the body of activated B cells, it significantly reduces the production of antibodies, including autoantibodies that can drive some autoimmune diseases. The indications for these important biologics are summarized in Table 9.1.

Rituximab is of interest because, in addition to its approved use in a range of B-cell malignancies, it also has extensive off-label use in multiple autoimmune diseases such as myasthenia gravis, Epstein–Barr virus, positive mucocutaneous ulcers, and idiopathic thrombocytopenic purpura. Indeed, wherever autoantibodies are the primary driver of inflammatory disease, there is logic behind its use. As biosimilar status can only be granted by regulators for approved

TABLE 9.1

Key biologics with approved indications for selected autoimmune diseases

Drug name	Mechanism of action	Drug class	Approved for selected inflammatory conditions Yes/No					
			Rheumatoid disease	Psoriatic arthritis	Ankylosing spondylitis	Psoriasis	Ulcerative colitis	Crohn's disease
Infliximab	TNFα inhibitor	mAb	Y	Y	Y	Y	Y	Y
Etanercept	TNFα inhibitor	mAb fragment – fusion protein	Y	Y	Y	Y	N	N
Adalimumab	TNFα inhibitor	mAb	Y	Y	Y	Y	Y	Y
Rituximab	Antibody to CD-20	mAb	Y	Y	Y	N	N	N

mAb, monoclonal antibody; TNFα inhibitor, inhibitor of tumor necrosis factor-alfa.
Data from drug monographs in the British National Formulary, 2023. bnf.nice.org.uk

indications, it becomes the responsibility of individual prescribers and formulary managers whether to permit the use of biosimilars of a drug in an off-label indication.

The medicines budget for biologic disease-modifying anti-inflammatory drugs can be substantial because the cost of each treatment is high (Table 9.2); because the course of treatment will typically require between 2 and 8 weekly intravenous infusions or subcutaneous injections over many years; and because such diseases are common. A 2023 paper by Conrad and colleagues looked at 19 of the most common autoimmune disorders, which together affected 10.2% of the UK population: 13.1% of women and 7.4% of men. Furthermore, the UK incidence rose by 4% over the study period (2000–2019). Adalimumab has been one of the top ten bestselling global medicines for many years, and the impact on medicines spending can be considerable. For example, in 2018, the UK spent £400 million per year (approximately US$ 514 million), making it a priority for biosimilar brand switching for the 46 000 patients on active treatment.[2]

Autoimmune diseases are an increasing problem for health services in the developing world through their association with increased economic development. For example, in the Middle East and North Africa (MENA) region of the WHO, the prevalence and annual incidence rate for rheumatoid disease increased by 28.3% and 25.2% between 1990 and 2019.[3] Similar trends are predicted for inflammatory bowel disease. Its prevalence is expected to increase between 2020 and 2035 by 1.5-fold for the WHO East Asia region with 4.5 million new cases; by 1.6-fold for high-income Asia-Pacific and Southeast Asia regions with 183 000 and 199 000 new cases, respectively; by 2.3-fold for the MENA region with 220 000 new cases; and to quadruple in India with 2.2 million new cases expected.[4]

Issues for formulary committees and prescribers

Budget impact. The rising prevalence of autoimmune diseases worldwide, the high cost of biologic response modifier medicines, and the long durations of treatment (often with schedules extending over many years) explain their significant impact on medicines' budgets.

TABLE 9.2

Cost of reference brand TNFα inhibitors for Crohn's disease in US$ – using list prices and dosing schedules for the USA from drugs.com for September 2023

Drug name	Form	Cost per unit	Typical dose schedules	Drug cost per dose for a 60 kg adult
Adalimumab reference brand Humira™	40 mg Pen for subcutaneous injection	US$ 3120/40 mg (when sold in a pack of 2)	160 mg week 0, 80 mg week 2, 40 mg week 4 and every 2 weeks thereafter	US$ 12 480 week 0; US$ 6240 week 2; US$ 3120 thereafter
Infliximab reference brand Remicade™	100 mg Vial for intravenous infusion	US$ 1239.21	5 mg/kg at weeks 0, 2, and 6, then every 8 weeks thereafter. May be increased to 10 mg/kg every 8 weeks in patients who have lost response	US$ 3717.63, rising to US$ 7435.26 for poor responders

Patients in the USA with health insurance may often get assistance or rebates to cover co-payments for prescription medicines after a threshold level has been crossed.
Adult weights vary – from 60 kg in Asia to 80 kg in the USA – which will impact infliximab costs, which follow weight-based dosing schedules, but not adalimumab, which has flat dosing.

Global biologic response modifier medicines sales ranged from US$5 to 16 billion annually (Table 9.3). Despite those budget implications, the WHO chose to include biologic response modifiers in their Lists of Essential Medicines from 2019. Both adalimumab and rituximab are given primary listing, while infliximab and etanercept have been listed as therapeutic equivalents of adalimumab.[5] Inclusion in the WHO list means that health systems should provide these medicines for free or at affordable prices. In line with past additions of biologic medicines to the Essential Medicines list, such as trastuzumab and rituximab, the WHO has always deferred inclusion until patents have expired on the originator reference biologic and biosimilar versions are expected.

Brand switching. Real-world evidence suggests that the greatest discounts for biosimilars are achieved when medicines are purchased in competitive annual tenders. Brand switching will be infrequent for short-duration treatments such as filgrastim, used to cover a typical 12–24 weeks of cytotoxic cancer chemotherapy. However, in inflammatory disease, where a biologic may be prescribed for 5 years or more, a patient may switch brands several times in that course. Surveys of physician and patient attitudes to biosimilars indicate that brand switching is a major area of concern. The anxiety focused on the potential for neutralizing anti-biosimilar antibodies to be induced by brand switching that could cause early treatment failure. This risk was potentially greatest for infliximab as this was the first monoclonal antibody biosimilar to be approved and because it was a murine-derived antibody rather than a human or humanized molecule.

Extrapolation. Many biologic response modifier medicines have multiple approved indications, with approval of the originator reference brand awarded as a result of pivotal clinical trials. In contrast, biosimilar medicines may be approved through extrapolation of indications. This means that prescribers may need to trust in the ‘sameness’ of the biosimilar in the absence of direct clinical data.

TABLE 9.3

Biosimilars for autoimmune disease approved to 2023 in Europe and the USA

Drug name	Original reference brand name	Date first biosimilars approved		Number of currently approved biosimilar brands		Global sales in the year before first biosimilar approval (US$)
		Europe	USA	Europe	USA	
Infliximab	Remicade™	2013	2016	4	4	6.7bn
Etanercept	Enbrel™	2016	2016	3	2	5.4bn
Adalimumab	Humira™	2017	2016	10	9	16.1bn
Rituximab	Mabthera™	2017	2018	5	3	7.6bn

Data for Biosimilars approved in Europe is from the Generics and Biosimilars Initiative, updated to 12 May 2023.[6]
Data for Biosimilars approved in the USA from drugs.com updated to 24 October 2023.[7]
Historic sales data are from Top Pharma listings on PM Live. pmlive.com/top_pharma_list.
The total of all EU currently approved biosimilars to 2023 is 76. Seventeen biosimilar approvals were withdrawn for marketing reasons after approval, including four adalimumab brands and two rituximab brands.
Regulatory approval dates in the USA may not correlate with first biosimilar launch dates due to patent disputes.
Not all countries share the same patent expiry dates. Furthermore, some regulators demand additional studies beyond those required in Europe and the USA. This explains why the availability of biosimilars may lag in different regions.

Real-world experience with biosimilars: UK

The UK National Health Service (NHS) is a single-payer, taxpayer-funded, comprehensive healthcare system with central policy making and health economic assessments and with regional management and payments directed through local commissioning groups.

Anti-TNF biologics cost the UK NHS a considerable amount, around £1 billion a year (€1.16bn; US$ 1.24bn). The first available biosimilar was infliximab, marketed in two bioidentical brands, Inflectra™ (Hospira) and Remsima™ (Napp pharma) that were approved in 2013. The first budget impact of biosimilars for the UK NHS was predicted to be £90 million recurring based on NHS spending of £184 million (€249m; US$ 279m) a year on originator reference brand infliximab (Remicade™) and 100% switching of patients, with the expectation of further returns as more reference brands lost patent protection over the next 5 years. The reality was that after 6 months, the biosimilar gained less than 5% of the market despite offering a 48% cut in price.[8]

The issue of extrapolation was felt to be significant for inflammatory bowel disease, made more difficult by negative position statements published by the European Crohn's and Colitis Organisation (ECCO) that questioned the validity of extrapolation of indications and claimed "switching from an established biologic to a biosimilar to save costs is likely to be as inappropriate and ineffective".[9] Yet inflammatory bowel disease is estimated to affect over 500 000 people in the UK and the budget impact of biosimilars could be significant.

This impasse was resolved through several steps:

1. A national audit by the UK Royal College of Physicians of 2722 adults and 278 children showed no difference in outcomes whether new patients were treated with biosimilars or the reference brand.[10]
2. The NOR-SWITCH randomized trial showed that switching from originator to biosimilar infliximab for five major indications in Norway had no significant difference at 52 weeks.[11]
3. The English NHS central administration introduced a specific commissioning framework for biological medicines. This permitted a 'gain-share' agreement where half of the financial savings from biosimilars were returned to the hospitals that achieved defined

targets of ≥80% switching of established patients and ≥90% for new treatment starts. For example, in Bristol UK, a switching program in 2015 saved £200 000 (€231 000; US$248 000) and, with a 50:50% gain-share agreement, provided £100 000 to be re-invested into local gastroenterology services, benefiting the patients and prescribers who made the changes and savings possible.[12]

4. Identification of a significant nocebo effect in the Danish infliximab biosimilar switch program led to the establishment of a centralized patient and prescriber information service for the NHS with help from biosimilar developers.[13] The nocebo problem has not been eliminated in the short term, but evidence that proactive measures can limit this have been shown in many health systems, for example, in infliximab switch programs from Melbourne, Australia.[14]

These lessons resolved uptake barriers, such that for subsequent biosimilar launches of etanercept, adalimumab and rituximab, switching rates of >80% were achieved within the first year of launch, making the UK NHS the fastest-adopting large nation healthcare system in Europe. Switching patients to biosimilars of these drugs led to significant cost savings: £99.4m for infliximab, £60.3m for etanercept, and £50.4m from rituximab biosimilars for a cumulative annual saving of £210.1m (€243m, US$ 260m).

By 2018, prescriber confidence was such that a UK nationwide campaign to drive biosimilars uptake across the NHS, which aimed to save £500 million (€578m, US$ 619m) a year by 2021, exceeded this target with efficiency savings of £800 million a year (€925m, US$ 991m). In addition, falling prices enabled reimbursement restrictions to be lifted such that more patients with milder levels of inflammatory bowel disease could receive biologics, increasing the treatment volume at lower total costs.

The issue of biosimilars in off-label indications was directly addressed by the UK National Institute for Health and Care Excellence (NICE). Using the logic that if the biosimilar was 'essentially the same' as the reference biologic, with the same pharmacology, immunogenicity, risks and benefits, then extrapolating biosimilars to use in unlabeled indications would be permitted. An example of this is the guidance for biosimilar rituximab for myasthenia gravis.[15]

Multi-winner tendering. The UK NHS has become concerned that single-winner tenders are detrimental to the long-term sustainability of biosimilars as a business model. Noting that long-term savings from generic medicines increased as the number of brands competed in the same market, the NHS tendering for adalimumab biosimilars resulted in five suppliers winning a share of the NHS market. This rewards multiple producers with income to repay the investment in biosimilar development and costs of launching in the UK, encouraging future biosimilar development. This process accepts that the maximum short-term financial savings from biosimilars may come at a detriment to future savings. Similar multi-winner tendering for biosimilars has been seen in Italy.[16]

Real world experience of biosimilars: Germany

In March 2024, approximately 31.0% of the German biopharmaceutical market was patent-free. Biosimilars accounted for 15.7% of all daily defined doses (DDD), representing half of all patent-free biopharmaceutical DDD and €517.4 million in sales. Knowledge of biosimilars among rheumatologists in Germany is high, and for immunological-related diseases, biosimilars now account for most of the delivered DDD of adalimumab (79.8%), etanercept (84.8%), infliximab (93.1%) and rituximab (92.8%). The exception to this is tocilizumab, used in the treatment of rheumatoid arthritis and giant cell arteritis, with biosimilars accounting for only 16.1% of DDD; however, biosimilars for tocilizumab were only recently approved by the EMA, in September 2023.[17]

German healthcare professionals share high confidence and institutional trust in the EMA to oversee a strict and thorough approval process for biosimilars entering the market. For its part, the EMA has provided extensive information regarding the safety and efficacy of biosimilars and educated healthcare providers on their approval processes. For rheumatic conditions, several well-designed comparative studies between biosimilars and their reference brands have also been conducted comparing single and double switching and have demonstrated no significant differences. Confidence in biosimilars among German patients is also perceived to be high.

The strong position of biosimilars in treating immunological-related diseases is also a result of favorable policies that have encouraged biosimilar uptake, generated awareness, and educated both patients and healthcare professionals on biosimilars. One such recommendation by the Task Force on the Use of Biosimilars to Treat Rheumatological Diseases was that of shared decision-making (SDM) involving the patient and healthcare professional.[18]

SDM is a joint decision made by the patient and their healthcare provider, considering the patient's values and priorities and the available treatment options. The use of SDM in rheumatologic diseases, particularly when biosimilars are available, has been actively encouraged and has been shown to reduce decision-making time when patients are involved.

The Outcome Measures in Rheumatology initiative has put forward a strategy to ensure successful SDM outcomes.[18] Such initiatives, especially for biosimilars, are essential for overcoming the nocebo effect. This effect was particularly prevalent in Germany during the initial introduction of biosimilars when awareness among healthcare providers was limited. Previous studies on switching to adalimumab, etanercept and infliximab biosimilars have demonstrated that discontinuation rates because of adverse effects or insufficient efficacy are higher in open-label studies than in double-blind studies, suggesting that the nocebo effect plays a role.[18] In the real-world setting, SDM may limit negative nocebo effects through improved patient knowledge of biosimilars.[19] Furthermore, using positive framing can also reduce the nocebo effect during switching.

Given the risk of the nocebo effect when treating rheumatologic diseases with biosimilars, switching to biosimilars should be made in the medical setting. Under these conditions, patients can benefit from positive framing and SDM. In Germany, the automatic substitution of reference biologics with biosimilars at pharmacies is currently under discussion; however, implementing such a policy may lead to a higher nocebo effect among patients.[18] A Danish study has previously demonstrated that automatic switching leads to an increase in the discontinuation rate of the biosimilar when compared to historical data.[20]

Overall, biosimilars in Germany and the field of rheumatology are now well-received and should serve as an example of what can be achieved through patient and healthcare provider education and awareness, which were seen as the main drivers of biosimilar use.

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10 Conclusions

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The 'biosimilar pathway' developed by the European Medicines Agency (EMA) follows the principles that apply following a change to the manufacturing of a biologic. Central to the pathway is the demonstration that there are no significant clinical differences between a biosimilar and its reference biologic based on analytical, preclinical and clinical data. Furthermore, demonstrating that the mechanism of action is the same in different conditions enables the biosimilar to be approved for the same indications as the reference biologic through extrapolation.

Biosimilars are subject to the same pharmacovigilance as their reference biologic. With almost two decades of use in Europe, no relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference biologics has been reported. There are currently 86 authorized biosimilars in the EU, and this number is expected to climb, with 120 reference biologics losing exclusivity in the coming decade. The EU, member states and organizations are actively encouraging biosimilar uptake through pricing and reimbursement policies and by strengthening trust and understanding among healthcare workers.

Crucial to adopting biosimilars are the decisions taken in drug and therapeutic meetings. Purchasers need to understand the biosimilar development and approval pathways and be able to differentiate biosimilars from intended copy biologics (ICBs). Selecting the best value biologic goes beyond price and includes product-, service- and patient-driven criteria. Prices can vary due to visible savings and confidential rebates.

Biosimilars are evaluated using stringent comparability assessments to demonstrate a clinical equivalence to the reference biologic without compromising efficacy and safety; however, there are follow-on biologics called ICBs that are not developed to biosimilar standards of the WHO and are found mainly in low- and middle-income countries (LMICs). By definition, an ICB misses out or underpowers one or more steps of the biosimilar regulatory pathway. ICBs and biosimilars are often challenging to differentiate, creating confusion and a lack of trust in the safety of biosimilars. These issues slow biosimilar uptake in LMICs, keeping prices high and restricting access.

Worldwide, the WHO and regulatory agencies have implemented strategies to strengthen biosimilar approval mechanisms and address legacy ICBs. Measures include standardizing nomenclature, encouraging short-term reliance on external regulatory authorities for biosimilar approvals, and pre-qualifying biosimilars. Most countries now have some form of biosimilar regulation; however, convergence to WHO standards has been slow, given that LMIC regulatory authorities are often resource-constrained.

The slow pace of adopting WHO standards creates conditions for the market entry of ICBs that hurt biosimilar trust among healthcare professionals. Without such standards, purchasers require vital data on the critical attributes of ICBs to make informed decisions; however, as discussed in this book, these data are lacking, resulting in less uptake of biosimilars and overall limiting the reach of life-saving biologics. Therefore, continued WHO policies are needed to educate healthcare professionals, foster trust in biosimilars, and shift LMIC regulations in line with best practices – as outlined in our practical steps.

Future developments in biosimilar regulation to watch. The comparative clinical trial is perhaps the most expensive and time-consuming part of biosimilar development. If it is truly the least sensitive step for detecting a clinically significant difference, then could future biosimilar regulations drop this requirement? Lower development costs and faster development times would be expected to lead to cheaper biosimilars, which in turn might make it attractive to develop biosimilars for orphan drugs as well as encourage smaller and less capitalized pharmaceutical manufacturers to enter the market.

There is already good evidence that for the vast majority of approved biosimilars, the comparative clinical trial added no significant information to the regulator's decision. An examination of 42 biosimilar programs showed that regulators rejected four due to quality issues. However, none failed approval due to purely efficacy differences.[1] Further support for this approach comes from the approval of three biosimilars in which the confirmatory clinical trial failed to reach the prespecified endpoints, but analytics could explain the differences in efficacy that were observed in the trial.[2]

In addition, the disparity between the lack of requirement for clinical testing following manufacturing process change but a mandatory requirement for biosimilars has become less tenable with more than a decade's experience with more than 70 approved biosimilars and over 2 billion patient-days' exposure during which no clinically significant difference has been seen, and no product has been recalled for safety or efficacy reasons.[3]

The first regulatory agency to signal its acceptance of such an approach was the UK Medicines and Healthcare Products Regulatory Agency. Their updated guidelines of May 2022 state:

> "Although each biosimilar development needs to be evaluated on a case-by-case basis, it is considered that, in most cases, a comparative efficacy trial may not be necessary if sound scientific rationale supports this approach."[4]

The US regulator is consulting on similar steps in September 2023 in a joint meeting with the International Pharmaceutical Regulators Program Biosimilars Working Group.[5] At that event, Dr Hye-Na Kang from the Norms and Standards Team at the WHO indicated a broad agreement in its review of scientific evidence and regulatory experience in 2020:

> "Current data could suggest that state-of-the-art analytical and functional testing and robust PK and PD studies are sufficient to demonstrate biosimilarity, whereas in vivo animal studies and large confirmatory efficacy and safety studies are generally not needed."

At the same meeting, the Chair of the European Medicines Agency (EMA) Biosimilar Medicinal Products Working Party, René Anour, explained that efficacy trials could be omitted if there were pharmacodynamic (PD) markers validated as a surrogate for efficacy. He identified two orphan biosimilars for eculizumab (Bekemv and Epysquli) developed on PD rather than clinical endpoints in small trials of patients with paroxysmal nocturnal hemoglobinuria. He announced the European regulator would issue a concept paper on the topic – but gave no likely publication date.[6]

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