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Biosimilars

Biosimilars in immune-mediated inflammatory diseases

Focus on the South African patient and clinical environment

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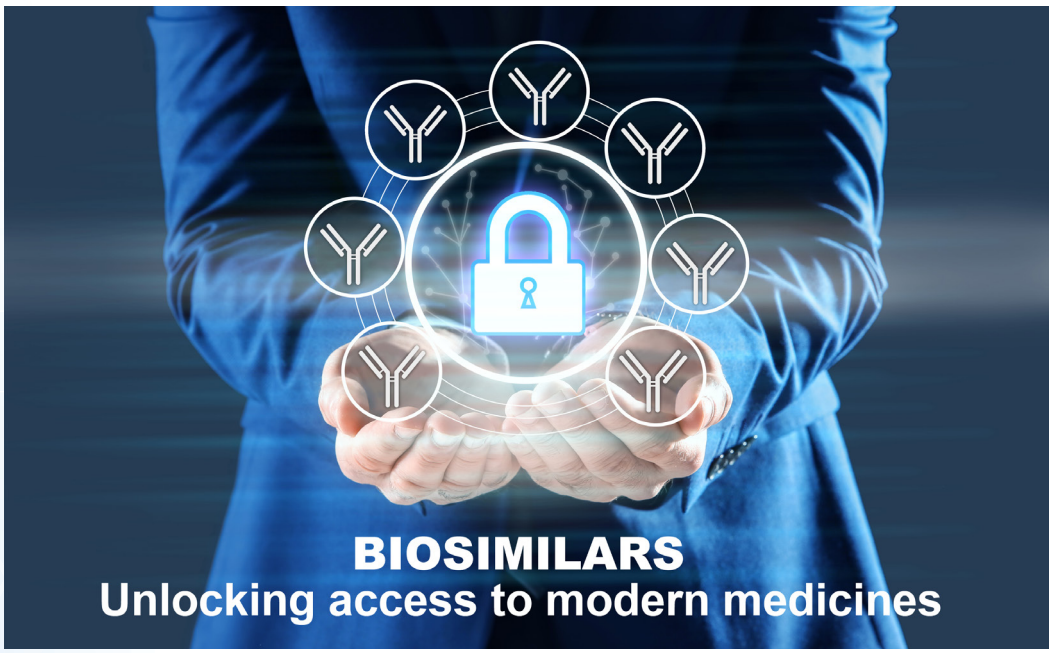
Learning objectives

You will learn:

- To understand the defining characteristics of biosimilars in terms of the originator biologic reference products (RPs)
- To understand the regulatory framework of evidence required to register a biosimilar in South African and European markets
- To encourage activism for the greater uptake of biosimilars for South African patients
- To provide up-to-date data on switching studies in immune-mediated inflammatory diseases (IMIDs) with regard to the efficacy and safety of biosimilars and their RPs, which have revolutionised the treatment of *inter alia* rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis and psoriatic arthritis.

Introduction

Improved understanding of the pathophysiology of IMIDs has provided targets for the development of biologic disease-modifying agents (DMARDs). Biologic DMARDs have transformed the treatment and outcomes of patients with these chronic and disabling conditions. Cytokine blockers were the first to be developed and include agents that act against TNF-α (etanercept, infliximab, adalimumab, golimumab and certolizumab), interleukin-6 (IL-6) receptor blockers (tocilizumab and sarilumab) and IL1-12/23 blockers (ustekinumab).



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Targeted synthetic disease-modifying agents, also known as small-molecule inhibitors, such as the JAK inhibitors (tofacitinib), are newer oral drugs that offer new convenience to IMID patients.

Multiple biosimilars have been licensed by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). There are currently more than 200 biosimilar candidates in development across the world and these will increasingly become available in middle-income countries such as South Africa.[1]

While there was initially some physician resistance to biosimilars,[2] this is being overcome and uptake is increasing globally.

In South Africa, biosimilars of infliximab and adalimumab are now available. Biosimilars of insulin have been available for some years.

What is a biosimilar?

Biosimilars are highly similar versions of reference biologics that have already been marketed and approved by regulatory agencies. There are no clinically meaningful differences between biosimilars and the reference biologics in terms of safety, potency and purity.[3] Reference biologics are more complex than small-molecule drugs, which can be copied as generics and thereafter proven bioequivalent in healthy volunteers.

The development of biosimilars requires sophisticated manufacturing processes that 'reverse engineer' the reference products (RPs), as details of these products are not publicly available. These involve cell culture and purification processes refined over time to produce a product that possesses the target profile.

"In essence, the production of a quality biosimilar is every bit as demanding as the manufacturing process of the original RP. The investment is 100 times that required to produce a generic product," Professor Reuter pointed out.

The goal of biosimilar development is to demonstrate that there are no clinically meaningful differences between the proposed biosimilar and the reference biologic – not to re-establish the clinical benefit of the latter (Table 1).[3]

Table 1. What are the similarities and differences between biosimilars and reference products?

	Originator	Biosimilar
Target definition	Receptor, surface antigen, effector molecule	Analyses of the variabilities of the originator over years, cell line and product development
Proof of similarity	NA	Complex analytics, functional tests
Preclinical	Bioassay, toxicology	Reduced programme
Pharmacokinetic and pharmacodynamic studies	PK and PD studies	Often larger PK and PD studies
Dose finding	Phase II studies	No Phase II studies
Phase III studies	All indications	1-2 indications

What is the development pathway for biosimilars and what are the criteria for South African registration?

The development of biosimilars follows a stepwise approach, moving from analytical analyses to non-clinical toxicology studies and clinical pharmacology studies showing pharmacokinetic and efficacy equivalence to the RP and demonstrating that the proposed biosimilar and RP share similar pharmacodynamic, immunogenicity, and safety profiles (Figure 1).

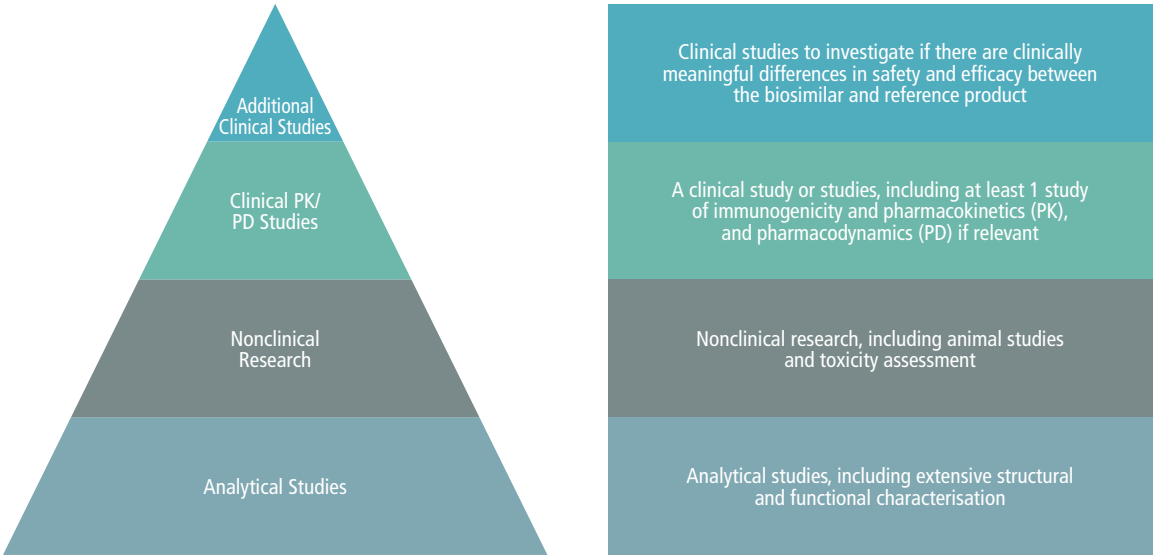

Figure 1. Biosimilar development pathway

While regulatory agency guidelines on biosimilars are scientifically aligned, they do vary in requirements and also in interpretation of the same data; most regulatory agencies recommend that discussions are held before and during the development of a biosimilar (Table 2).[4]

Table 2. US FDA, EMA, and SAHPRA requirements for data supporting biosimilar approval[4]

Type of data[a]	US FDA	EMA	SAHPRA
Structural and analytical studies	✓	✓	✓
Functional assays[b]	✓	✓	✓
In vivo toxicology	✓	Dependent on *in vitro* findings	Dependent on *in vitro* findings
Clinical pharmacokinetic study	✓[c]	✓	✓
Clinical immunogenicity assessment	✓	✓	✓
Clinical efficacy and safety trials	Required in the absence of surrogate pharmacokinetic markers for efficacy		
Clinical switching study	Required to demonstrate interchangeability[d]	✗	✘

US FDA: United States Food and Drug Administration
EMA: European Medicines Agency
SAHPRA: South African Health Products Regulatory Authority
[a] In all cases, data should be collected in a comparative fashion between the proposed biosimilar and the RP
[b] The FDA states that the functional assays can be *in vitro* and/or *in vivo,* whereas the EMA requires *in vitro* functional assays
[c] The FDA requires at least one clinical pharmacokinetic study to compare the proposed biosimilar with the version of the RP licensed in the USA
[d] Switching studies are not required for the FDA biosimilar approval pathway *per se.* However, one or more switching studies would generally be required as part of a demonstration of interchangeability. These studies should evaluate changes in treatment resulting from two or more alternating exposures to the RP and the proposed interchangeable biosimilar

Note: Biosimilar medicine requirements are available on the SAHPRA website

Interchangeability and switching from a RP to a biosimilar

Interchangeability refers to the possibility of exchanging one medication for another that is expected to have similar clinical effects. This could mean switching from a RP to a biosimilar or replacing one biosimilar with another. The South African regulatory agency and many other regulatory agencies, such as the EMA, do not require clinical switching studies for biosimilar registration purposes. They require, if a surrogate marker of efficacy is not available (and this is true of IMIDs), a comparative clinical trial to demonstrate clinical comparability between the biosimilar and the RP.

The US FDA is an exception to this, requiring a single transition evaluation to demonstrate that a biosimilar can be switched with a RP.

Switching studies should be designed with scientifically sound approaches to provide the highest level of evidence so that a RP can be effectively switched to a biosimilar by the clinician (Table 3).[5] In South Africa, pharmacy-based switching of RPs to biosimilars or between biosimilars is not allowed.

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Table 3. Optimal switching study design[5]

1. Randomised design with appropriate control arms
2. At least one-way switch from originator to biosimilar
3. Assessment of immunogenicity
4. Sufficient washout between treatment (multiple switching)
5. Sufficient power to assess efficacy, safety and equivalence
6. Sufficient follow-up period.

These studies can be transitional over time, with a single switch from one treatment to another, or switch studies that are crossover in design with each patient receiving the RF and the biosimilar sequentially (Figure 2).[5] Clinical experience with biosimilars for IMIDs is growing; it currently exceeds 700 million patient-days and biosimilar uptake is increasing globally.[6]

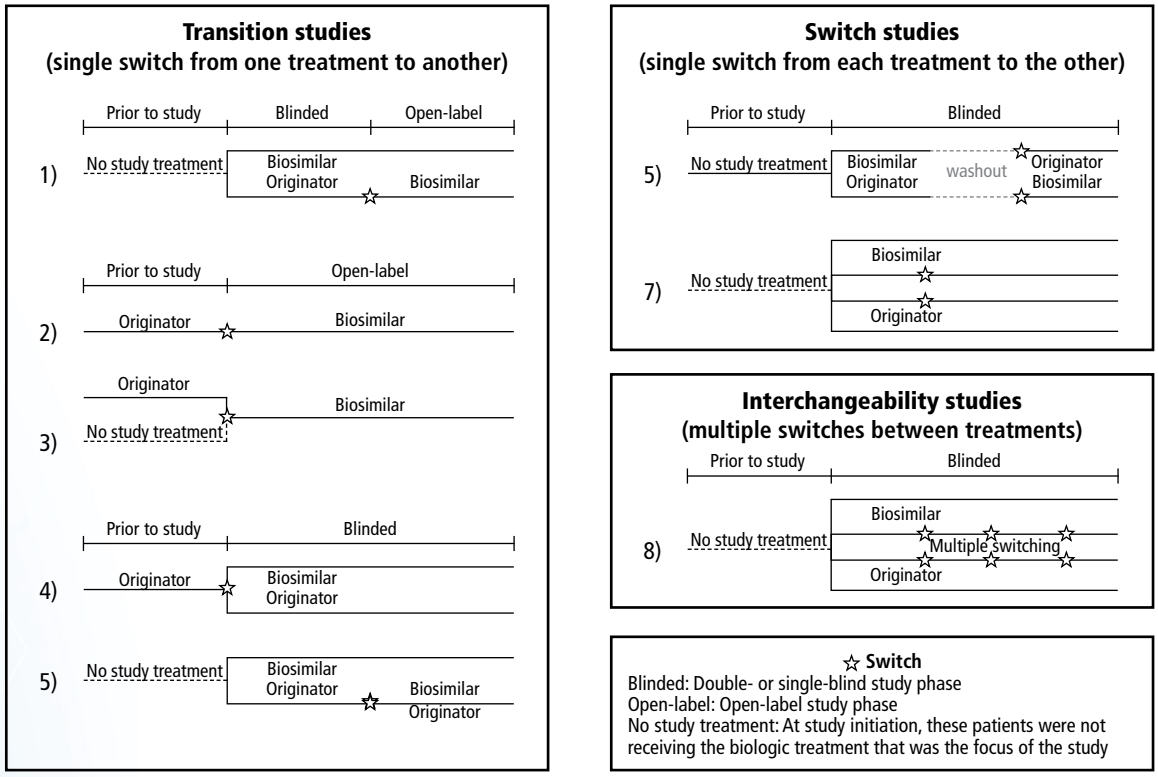

Figure 2. Switching study designs[5]

Clinical experience with biosimilars for IMIDs is growing; it currently exceeds 700 million patient-days and biosimilar uptake is increasing globally

Switching studies are confined to approved indications for the RPs. Some anti-TNF products and their approved indications are listed in Table 4. Switching studies may not be undertaken for all indications, but once biosimilarity is proven in switching studies in a particular clinical indication, e.g. rheumatoid arthritis, then extrapolation to other indications that have already been approved for the RP can be granted by the regulatory authority. "Individual clinicians may, on the basis of successful switching studies that confirm efficacy and safety in one IMID that they treat in their speciality area, e.g. rheumatology, gastroenterology or dermatology, be willing and confident enough to introduce these biosimilars to patients with related conditions for which the RP has already been approved," Professor Reuter noted.

Extrapolation is an accepted scientific and regulatory principle that clinicians may also be willing to support based on real-world experience derived from registries and post-marketing adverse event records.

A recent systematic review of the efficacy and safety of switching patients between reference and biosimilar infliximab assessed all scientific publications from 2004 to 2018.[7] These publications included patients with IMIDs such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.

Data from six randomised controlled trials were identified; the remaining 64 studies were observational ones. The majority of trials involved a single switch between the RP and the biosimilar. This systematic review found that no significant risks were identified with biosimilar use relative to the RPs; no clinically important efficacy or safety signals were associated with switching.

Table 4. Approved indications for anti-TNF products

	Infliximab	Etanercept	Adalimumab	Ustekinumab	Golimumab
Rheumatoid arthritis	X	X	X		X
Juvenile idiopathic arthritis		X	X		
Psoriatic arthritis	X	X	X	X	X
Axial spondyloarthritis	X	X	X		X
Crohn's disease	X		X	X	
Paediatric Crohn's disease	X		X	X	
Ulcerative colitis	X		X		X
Paediatric ulcerative colitis	X		X		
Plaque psoriasis	X	X	X	X	
Hidradenitis suppurativa			X		
Uveitis			X		X

The role of registries in monitoring biologics and biosimilars – the South African situation

"Individual clinicians may, on the basis of successful switching studies that confirm efficacy and safety in one IMID that they treat in their speciality area, e.g. rheumatology, gastroenterology or dermatology, be willing and confident enough to introduce these biosimilars to patients with related conditions." Professor Reuter

Registries worldwide have provided important real-world evidence related particularly to adverse events, e.g. increased risk of infections, lymphoproliferative malignancies, and cardiovascular disease associated with the use of biologics, both RPs and biosimilars.[8] In South Africa, the South African Rheumatism and Arthritis Association runs the South African Biologics Registry, which has provided valuable information on the risk of tuberculosis in users of biologics for rheumatic disease in a high-risk tuberculosis environment.[9]

It is envisaged that as registered biosimilars become increasingly available in South Africa, this registry will play an important role in local ongoing surveillance of these entities. This is in addition to the normal adverse events pharmacovigilance required by the South African authorities.

Clinician and patient support programmes – strategies to improve access to biologics and biosimilars in IMIDs

Biosimilar competition can create several advantages for the South African health care system as it is expected to increase patient access to safe and effective biological medicines of proven quality. They are expected to be less expensive due to their tailored development programme that builds on existing knowledge gained with the RPs. This avoids unnecessary repetition of non-clinical and clinical studies.

For information on what a biosimilar is and how safety and efficacy can be ensured, patients can download a patient-friendly document from the SARAA and SAHPRA websites.

Key learnings

- There are no clinically meaningful differences between biosimilars and the original reference biologics in terms of safety, potency and purity
- Switching studies should be designed with scientifically sound approaches to provide the highest level of evidence so that a RP can be effectively switched to a biosimilar
- Clinical experience with biosimilars for IMIDs is growing; it currently exceeds 700 million patient-days
- Registries worldwide have provided important real-world evidence related particularly to adverse events associated with the use of biologics, both RPs and biosimilars.

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