FACTSHEET

BIOSIMILARS

Biosimilars are pharmaceutical products that are almost identical copies of existing medicines.

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CANCER ALLIANCE

Collective South African Voices for Cancer

CONTENTS

What are biosimilars? 3

Regulation of pharmaceuticals: Safety, Quality and Efficacy (SQE) profile of biosimilars 4

Use of biosimilars in high income countries 7

Access issues related to biosimilars 8

Use of biologics in other low-to-middle income countries . . . 9

Biosimilars in South Africa 10

WHAT ARE BIOSIMILARS?

These are large pharmaceutical molecules of a biological nature that are developed after, and based on, the original, innovative biological[1]. In the case of small, synthetic molecules (which are standard medicine), the innovative molecule is known as the original or innovator, and the follow-on copy products made after the original patent has expired are known as generics.

Synthetic chemistry allows for the manufacturing of the exact same active ingredient. Biosimilars, however, cannot be defined as generics; it is not mandatory for the patent-holding company to share the details of their manufacturing process, so a deviation as seemingly minor as the temperature of the room in which manufacturing occurs will result in a slightly different molecule being produced because there is always variability in a live biological system. Biosimilar monoclonal antibodies (mAbs), a class of biosimilars, differ from other biosimilars in that they are large complex proteins used by the body's immune system to identify and neutralize entities that the body deems foreign. These are often disease-causing organisms such as bacteria and viruses. Biosimilar mAbs are usually administered in the treatment of diseases such as cancer or rheumatoid arthritis[2]. Biosimilar mAbs are easy to identify in that their names all end in the stem -mab[3].

Biosimilars are also known as similar biotherapeutic products (World Health Organization), similar biological products (European Union), subsequent entry products (Canada), similar biologics (India) and follow-on biological products[4].

1. https://badgut.org/wp-content/uploads/GIS-PIH-BI.pdf
2. https://www.mabxience.com/blogs/what-are-mabs-biosimilars/
3. https://www.who.int/medicines/services/inn/Revised_mAb_nomenclature_scheme.pdf
4. https://www.tga.gov.au/sites/default/files/biosimilar-medicines-regulation.pdf

REGULATION OF PHARMACEUTICALS: SAFETY, QUALITY AND EFFICACY (SQE) PROFILE OF BIOSIMILARS

The South African Health Products Regulatory Authority (SAHPRA), formerly known as the South African Medicines Control Council (MCC) and the National Department of Health (DOH) have published a document[5] meant to provide guidance to would-be registrants of biosimilar medicines.

5. https://www.sahpra.org.za/documents/d259816c2.30_biosimilars_aug14_v3.pdf

On the 3 tenets of the International Council on Harmonisation (ICH)[6] – safety, quality, and efficacy as compared to the innovator biological- South African regulations are as follows:

CLINICAL SAFETY OF THE BIOSIMILAR

This involves a study in the differences in the safety profiles of the originator versus the biosimilar. The nature, severity and frequency of adverse reactions is observed. As these molecules are of a biological nature, the immunogenicity of the product i.e. its ability to provoke an immune response in the body must be studied. This is because the impact of the body's immune response affects the bioavailability and clearance (elimination) of the medicine, directly influencing its dose-response profile. This calls for the consideration of immunogenicity in events such as hypersensitivity and autoimmunity, among others.

QUALITY OF THE BIOSIMILAR

The biosimilar active pharmaceutical ingredient (API) must not have any detectable, relevant differences in its physiochemical characteristics when compared to the biological API. A full dossier is to accompany the registration application detailing the source materials as well as the inactive pharmaceutical ingredients (IPIs), the manufacturing process, its stability and the control of the process in accordance to various manufacturing guidelines, including the South African Guide to Good Manufacturing Practices[7]

EFFICACY OF THE BIOSIMILAR

The purpose of efficacy studies is to display clinical comparability between a biosimilar and its reference biological medicine. This includes the pharmacokinetic profiles (absorption, distribution, elimination of product) and the pharmacodynamic profiles (therapeutic efficacy). These comparisons must be made in a population in which possible differences in therapeutic outcome and side-effect incidences may be clearly observed. Equivalence in exposure and effect is desired.

6. https://www.ich.org/products/guidelines.html
7. https://www.sahpra.org.za/documents/16b9955c4.01SAGuidetoGMPJun10v5.pdf

INTERCHANGEABILITY

This is not yet relevant to biosimilars in South Africa but it is worth a look into as it is highly likely to feature in future discourse. SAHPRA has a document specifically addressing the substitution of medicines[8] published in April 2010. The recommendations, targeted at prescribers and medication administrators, state that as biosimilars cannot be classified as generics (as they cannot be identical to their reference products) and sometimes have clinical indications different from their reference biologicals, they cannot be considered interchangeable with the originator product, or products within the same class. Automatic substitution, as stated in Section 22F (Generic substitution) of the Medicines and Related Substances Act 101 of 1965[9], therefore does not apply to biosimilars as emphasis is placed on treatment choices being in the patient's interest in terms of safety, quality and efficacy.

The WHO guideline[10] also specifically stipulates that biosimilars are not interchangeable with their reference products. Despite this a few national regulatory authorities in Europe such as The Netherlands and Finland do allow substitution of biosimilars for their reference medicines, albeit under special conditions.

- In The Netherlands, substitution is allowed only with sufficient clinical monitoring and only after the patient has been informed and they have consented[11].
- In Finland, it is permitted but must take place under supervision of a healthcare professional[12].
- In France, provisions in the law that allow the substitution of originators by generics have been adapted to extend to biosimilars; however, it has still to be enacted and consequently has not been implemented yet[13].

8. https://www.sahpra.org.za/documents/cd5208122.10_Substitution_of_medicines_Jan10_v2.pdf
9. https://www.hpcsa.co.za/Uploads/editor/UserFiles/downloads/legislations/acts/medicines_and_related_sub_act_101_of_1965.pdf
10. https://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1
11. http://gabionline.net/Biosimilars/General/Dutch-medicines-agency-says-biosimilars-have-no-relevant-differences-to-originators
12. http://www.gabionline.net/Policies-Legislation/Finnish-drug-regulator-recommends-interchangeability-of-biosimilars
13. http://www.gabionline.net/Policies-Legislation/France-to-allow-biosimilars-substitution

USE OF BIOSIMILARS IN HIGH INCOME COUNTRIES

UNITED STATES OF AMERICA (USA)

According to the Food and Drug Administration (FDA), the approval of biosimilars can improve access to care for patients by increasing the number of medication options and potentially lower costs[14]. There are currently 23 biosimilars approved for use in the USA. Of those 23, 2 are trastuzumab generics. Trastuzumab is a biological medicine used in the treatment of HER2+ breast cancer[15]. Trastuzumab has been shown to be cost-inaccessible in South Africa, which is to say that it is difficult to attain due to its high cost[16].

CANADA

The Biologics and Genetic Therapies Directorate (BGTD) is the Canadian regulatory authority of biological medicines and radiopharmaceuticals for human use in Canada[17]. As of 14 December 2018, the BGTD has 10 approved biosimilars[18].

EUROPE

The European Medicines Agency (EMA) is responsible for evaluating the majority of market authorization applications (MAAs) prior to their approval and marketing in the EU[19]. Legislation on medicines including biologicals was passed into law in 2001 (Directive 2001/84/EC)[20] and subsequently the first guidelines for biosimilars were introduced in 2005. Between then and January 2019, 50 biosimilars have received market authorization[21],[22]

14. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information
15. https://www.breastcancer.org/treatment/targeted_therapies/herceptin
16. https://www.canceralliance.co.za/wp-content/uploads/2018/08/Breast-Cancer-and-Trastuzumab-Fact-Sheet-8-August-2018.pdf
17. https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch/biologics-genetic-therapies-directorate.html#Biologics
18. http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Canada
19. https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview
20. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/directive-2001/83/ec-european-parliament-council-6-november-2001-community-code-relating-medicinal-products-human-use_en.pdf
21. http://www.gabionline.net/Reports/Use-of-biosimilars-in-oncology-in-Europe
22. http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe

ACCESS ISSUES RELATED TO BIOSIMILARS

Biosimilars were developed as an attempt to address the issue of cost-inaccessibility to life-saving, quality-of-life improving, but highly expensive biological medicines[23]. Biosimilar competition should improve patient access to safe and effective biological medicines that have proven safety, quality and efficacy[14].

23. https://www.who.int/en/news-room/detail/04-05-2017-who-to-begin-pilot-prequalification-of-biosimilars-for-cancer-treatment

USE OF BIOLOGICS IN OTHER LOW-TO-MIDDLE INCOME COUNTRIES

INDIA

There are more than 100 Indian biopharmaceutical companies in the business of manufacturing and marketing biosimilars[24]. The Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology (DBT) developed "Guidelines on Similar Biologics; Regulatory Requirements for Marketing Authorization in India" in 2012 and revised them in 2016[25]. More than 50 similar biologics have been approved and marketed in India[26] since, and this number continues to grow as more patents for biologicals are expected to expire in the next few years, thereby opening the market up to the entry of biosimilars and increasing patient access to these products as there will be market share competition and therefore more patient-friendly pricing if these companies are to make significant sales from their innovations.

24. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6394151/
25. http://bch.cbd.int/database/attachment/?id=19050
26. http://www.gabionline.net/Biosimilars/General/Similar-biologics-approved-and-marketed-in-India

BIOSIMILARS IN SOUTH AFRICA

South Africa's first biosimilar was authorized five years after it first sought regulatory approval.[27] Cipla, in collaboration with Teva Pharmaceutical Industries Ltd, launched Filgrastim Teva in 2018.

Filgrastim is used as supportive treatment to counter neutropenia, a major side-effect to chemotherapy that results due to the disruption of the production of immune cells in the bone marrow of patients.[28]

The first monoclonal antibody biosimilar to be registered in South Africa was trastuzumab. Ogivri® manufactured by Biocon, with Mylan as the Applicant, was approved by SAHPRA on 15 May 2019. This has opened up competition and will begin to effectively shape South African market access for the future.

At least another four trastuzumab biosimilars are awaiting approval at SAHPRA. [29]

27. https://www.medicalbrief.co.za/archives/teva-launches-first-biosimilar-drug-sa/
28. https://www.bizcommunity.com/Article/196/335/180258.html
29. https://canceralliance.co.za/motivation-for-the-prompt-approval-of-trastuzumab-biosimilars-to-promote-competition-in-the-market/

REGISTRATION OF BIOSIMILARS

The guideline for biosimilars applies only to those biologicals composed of well-characterized recombinant DNA-derived therapeutic proteins. It excludes vaccines, even if these are derived from recombinant DNA technology.[30]

This guideline is based on two source guidelines – those of the EMA and WHO. Before registration approval, proof of efficiency of the biosimilar and safety in human use must be indicated.

A reference biological that is registered within South Arica (on the basis of safety and efficacy) is used in a head-to-head comparative study. The reference biological medicine is the innovator medicine, for example- filgrastim was used to compare Filgrastim Teva to, prior to approval. The quality of the medicine, as well as clinical and non-clinical studies were compared to demonstrate similarity.

The samples of the reference product used in comparability studies do not need to be procured from the South African market but can be sourced from a country with which SAHPRA is aligned, and these would be countries with stringent regulatory systems as influenced by ICH, as well as Australia, Canada and Switzerland.

Specific requirements for safety, quality and efficacy are briefly reviewed below.[5, 29]

CLINICAL REQUIREMENTS

Clinical comparability studies should only proceed after acceptable biosimilarity has been established at a physicochemical level (non-clinical studies). The clinical comparability exercise involves pharmacokinetic (movement of the medicine within the body – absorption, distribution, elimination) and pharmacodynamic (effect of the medicine on the body) studies followed by clinical efficacy and safety trials. Generally, an equivalence trial design is preferred although other designs could be acceptable if properly motivated and justified. A patient population that is highly sensitive should be selected and the patient population should be large enough to detect significant differences in safety, efficacy and immunogenicity.

30. http://gabi-journal.net/regulatory-requirements-for-the-development-and-registration-of-biosimilars-in-south-africa.html#R1

For each indication for which the reference product is authorized, clinical studies should be done on the biosimilar. In cases where the clinical effects have the same underlying mechanism of action, data from a clinical trial of the biosimilar in one indication may be used to support approval of the biosimilar for other indications for which the reference medicine is approved.

Preregistration safety data, derived from the efficacy trials, should be obtained to address the adverse effect profiles of the biosimilar and reference medicines. Post-approval pharmacovigilance is also required, accompanied by the submission of regular periodic safety update reports (PSURs) to SAHPRA. This is a condition of the registration of all new biologicals, including biosimilars.

A suitable Risk Management Plan (RMP) for monitoring immunogenicity, inherent safety concerns and unknown safety signals that could result from the impurity profile and other properties of the biosimilar, should be submitted at the time of application for registration of the biosimilar product.

NON-CLINICAL REQUIREMENTS

Non-clinical studies are designed to detect differences between the biosimilar seeking approval and its reference medicine. Ideally, they should be conducted before initiation of clinical investigations so as to save on time and resources in the event that the differences are too significant.

These studies should be comparative, monitoring endpoints such as pharmacodynamic effects and toxic effects (linked to clearance of the medicine from systemic circulation), as determined in at least one repeat dose study.

Toxicokinetic measurements should be included and must involve analysis of immunogenicity as this would be of value in demonstrating similarity of immune responses to both reference and biosimilar products. Important to note - animal immunogenicity studies cannot serve as an alternative to immunogenicity studies in humans. In general, other routine toxicological studies such as safety pharmacology, reproduction pharmacology, mutagenicity and carcinogenicity studies are not required for biosimilar medicines. If the minimum required data can be obtained with in vitro biological assays, then these should be used or considered. Justification will, however, be required.

QUALITY REQUIREMENTS

A full quality data dossier with the following details pertaining to the biosimilar API must be submitted:

- the structural characteristics
- the chemical and physical properties
- its validated manufacturing and control processes
- its stability profile

Moreover, with regard to the final product, the following data must be included:

- the formulation of the final product
- the manufacturing process
- filling and packaging procedures
- the stability profile of the final product

These data for the biosimilar must be equivalent in amount and extent to that required for the registration of the innovator.

In the case of biosimilar mAbs, the process is more specific and more stringent (Annex 1[5]).

REGISTRATION PIPELINE

As already mentioned, Filgrastim Teva is the first biosimilar to be registered in South Africa. Based on the Cancer Alliance report on barriers to access published in 2017[31], the following would be biologics the registration of whose biosimilars would be of interest:

BIOLOGIC	INDICATION	MANUFACTURER	AVAILABILITY OF BIOSIMILARS
Rituximab	Treatment of B-cell non-Hodgkin lymphomas	Roche	Yes – Europe19, India23, USA11
Trastuzumab	Treatment of HER2+ breast cancer	Roche	Yes – Europe19, India23, USA11
Ipilimumab	Treatment of metastatic melanoma	Bristol-Myers Squibb	No - Extended patent protection expires in 2022[32]
Bevacizumab	Treatment for colorectal, kidney and lung cancers	Roche	Yes – Canada15, Europe19, India23, USA11

31. https://www.canceralliance.co.za/wp-content/uploads/2018/02/Exploring-Patent-Barriers-to-Cancer-Treatment-Access-in-SA-24-Medicine-Case-Studies-October-2017-update-January-2018.pdf
32. https://www.protagenproteinservices.com/biopharmaceuticals/biosimilars#ipilimumab