Biologics: Targets and Therapy

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REVIEW

# Biosimilars: Science, Implications, and Potential Outlooks in the Middle East and Africa

Radwa Ahmed Batran[1], Mai Elmoshneb[1], Ahmed Salah Hussein[1,2], Omar M Hussien[1], Fady Adel[1], Reham Elgarhy[1], Mosaad I Morsi[1]

[1]Medical Affairs Department, RAY Contract Research Organization, Giza, Egypt; [2]Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Correspondence: Ahmed Salah Hussein, Faculty of Medicine, Al-Azhar University, Cairo, Egypt, Tel +20 1158276261, Email ahmedsalah2230@azhar.edu.eg

**Abstract:** Biosimilars are biological products that efficiently replicate the function of the originator products. They have changed the prognosis of millions of patients with many serious conditions. The main engine beyond their development is to bring competition into the marketplace, accordingly further the healthcare systems' sustainability. Furthermore, by lowering financial obstacles to biological treatments, biosimilars play a critical role in budgetary redistribution and, hence, promote better allocation of scarce healthcare resources. Today, biosimilars have become a substantial component of effective biological therapies anywhere in the world. Alike, most Middle East and African countries are encouraging the domestic biosimilars industry, and the whole region is aware of the biosimilars' importance. However, constraints to increasing biosimilars uptake should be addressed.

**Keywords:** biologics, biosimilars, comparability, efficacy, immunogenicity, safety, Middle East, Africa

## Biosimilars Landscape

Biosimilars are biologic agents with no clinical differences from the original reference product. They have an important role in cancer treatment, as they have launched in the marketplace with a reduced price to increase patient access to their treatment and give the health providers and the patients many therapeutic choices. The regulatory authorities have set requirements for biosimilar product approval based on comprehensive non-clinical and analytical comparisons with the original reference medication (eg, post-translational modifications) that are important to the function of the similarity between the biosimilar and original reference medication. Then, the clinical development process is followed to assess the efficacy, pharmacodynamics, pharmacokinetics, immunogenicity, and safety. The equivalence in one indication of the biosimilar product may allow the assumption of all the indications of the original reference product. Recently many trastuzumab biosimilars are providing an example of how this process benefits the patients, healthcare providers, and payers.[1–4]

Switching treatment from the original reference product to a biosimilar is supported by most available data, predominantly from indications other than cancer. Post-marketing surveillance programs will be required to ensure optimal pharmacovigilance reporting. Biosimilars differ from generic small-molecule drugs in many aspects, including manufacturing processes that are unique from their original reference medication and the complexity of these molecules. These differences may affect biosimilars through post-translational modifications that can occur in specific cellular production lines, and these modifications have prospective effects on protein structure, function, clinical pharmacology, and immunogenicity.[1,2,5] Although the biosimilar has to be very similar to the original reference medication, minor differences in the inactive components are allowed, as long as there are no clinically meaningful differences in purity, potency or safety, or quality, safety and efficacy compared with the original reference product.[1,6]

Biologic drugs are a vital element of cancer treatment. Unlike traditional pharmaceutical drugs, which are small molecules, biologics are large molecules originating from living organisms or recombinant proteins produced by cells transformed with the genetic information encoding the corresponding protein.[7] They are proteins with a complex

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structure used as therapeutics. In contrast to the small molecule drugs, they are not chemically synthesized depending on the living host systems – which are animal or human cells – making the process of biologic production strongly controlled and more complex than chemical manufacturing. Consequently, biologics are expensive to develop and manufacture, and the treatment costs are usually high. The three biggest-selling cancer treatments of 2015 were all monoclonal antibody- biologics: bevacizumab, trastuzumab, and rituximab,[8] which elaborate on the importance of the biologics. At that time, they were under patent protection. However, when the patent protection of these biologics has expired, the biosimilar forms of each molecule become available in the marketplace and ready for competition with their reference biologics. According to the United States Food and Drug Administration (US FDA), a biosimilar is a biologic product that is highly similar to and has no clinically meaningful differences from the approved reference originator medication.[6] A similar definition is provided by the European Medicines Agency (EMA), which defines a biosimilar as

> A biosimilar is a biological medicine highly similar to another already approved biological medicine (the 'reference medicine'). Biosimilars are approved according to pharmaceutical quality, safety and efficacy standards that apply to all biological medicines.[9]

The entry of biosimilars into the oncology marketplace offers many advantages for the benefits of the patients, the healthcare providers, and the biopharmaceutical field to innovate more biological therapies and their biosimilars to increase the patient's accessibility to their biologic products with a low price and giving the physicians many choices to select the most convenient therapy for the patient. Moreover, the availability of biosimilars in the marketplace may open the door for biological medicine to be administered and dispensed for the patients that are in need in many countries where the price of the medication is considered a priority and one of the challenges that may obstacle the patients to reach their medications.[10] Hence, the benefits of the biosimilars will be entirely fulfilled with the strict and rigid regulatory obligations and demands in the developing countries.[11] When the replicates are below the standard (ie, do not fit the required criteria) or accompanied by undermined safety measures that can affect the patient's health in some areas, they will never be accepted or get the required approvals in advanced countries like the European Union (EU) and the United States of America (USA).[7,8] Still, the advanced countries have some worries and misunderstandings about using biosimilars because they are not identical to the original biologic product. Therefore, demonstrating the full illustration of the rigid and strict development process and approvals of the biosimilars would remove these worries regarding their use. In this review, we explain and elaborate on biosimilars' development and approval process, focusing on the oncology biosimilars in the breast cancer therapeutic area, for example, the trastuzumab biosimilar. The experiences gained from this example in cancer treatment have been implemented in many other biosimilars serving other therapeutic areas.[1,12]

The US FDA has approved biosimilar medications to treat many other conditions than cancer, such as diabetes, chronic skin and bowel diseases (like psoriasis, irritable bowel syndrome, Crohn's disease, and colitis), arthritis, kidney conditions, and various inflammatory and autoimmune diseases.[13] By May 2022, eleven biological agents: bevacizumab, etanercept, epoetin-alfa, trastuzumab, adalimumab, pegfilgrastim, filgrastim, infliximab, rituximab, insulin glargine, and ranibizumab have been used as reference products for the approval of 36 biosimilar agents (Table 1). Moreover, new biosimilars are currently still being FDA approved, with the most recent approval granted for the biosimilar agent pegfilgrastim-pbbk, which is used to decrease the incidence of febrile neutropenia in subjects treated with chemotherapy.[14,15]

## Overview of Biosimilars Development Pathway

Biosimilars are exposed to a sequence of approvals that may require many approaches and a lot of steps, as for the generic medications, to improve the patient's access to their prescribed medication with a low cost and short duration. However, the process to illustrate the similarity between the biosimilar and the originator is very sophisticated despite the process needed to demonstrate the same efficacy and safety measures of the generic product. Therefore, the EMA and the FDA have recommended some requirements to get the biosimilars approval that confirms the biosimilarity and the original biologic product, followed by the permission of the regulatory and commercializing authorities to promote the biosimilar agents in the market.[16] That includes different types of studies utilizing similar doses, starting from the analytical study that should be

**Table 1** Summary of the FDA-Approved Biosimilars

| Drug Class | Reference Product | Indications | Biosimilar(s) | FDA Approval Date |
|---|---|---|---|---|
| TNF Blockers | Etanercept | Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis | Etanercept-ykro | April, 2019 |
| | | | Etanercept-szzs | August, 2016 |
| | Adalimumab | Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, Crohn disease, ulcerative colitis | Adalimumab-fkjp | July, 2020 |
| | | | Adalimumab-afzb | November, 2019 |
| | | | Adalimumab-bwwd | July, 2019 |
| | | | Adalimumab-adaz | October, 2018 |
| | | | Adalimumab-adbm | August, 2017 |
| | | | Adalimumab-aqvh | December, 2021 |
| | Infliximab | Crohn disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, plaque psoriasis | Infliximab-axxq | December, 2019 |
| | | | Infliximab-qbtx | December, 2017 |
| | | | Infliximab-abda | April, 2017 |
| | | | Infliximab-dyyb | April, 2016 |
| Anti-VEGFA monoclonal antibody | Bevacizumab | Metastatic colorectal cancer, non-small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer | Bevacizumab-bvzr | June, 2019 |
| | | | Bevacizumab-awwb | September, 2017 |
| | | | Bevacizumab-maly | April, 2022 |
| | Ranibizumab | Treatment of several eye diseases and conditions, including nAMD (wet), macular edema (fluid build-up) following retinal vein occlusion, and myopic choroidal neovascularization | Ranibizumab-nuna | September, 2021 |
| ESA | Epoetin alfa | Anemia caused by CKD, chemotherapy, or zidovudine use in HIV patients | Epoetin alfa-epbx | May, 2018 |
| HER2/neu receptor antagonist | Trastuzumab | HER2-associated breast cancer, HER2-associated gastric (metastatic) or gastroesophageal junction adenocarcinoma | Trastuzumab-anns | June, 2019 |
| | | | Trastuzumab-qyyp | March, 2019 |
| | | | Trastuzumab-dttb | January, 2019 |
| | | | Trastuzumab-pkrb | December, 2018 |
| | | | Trastuzumab-dkst | December, 2017 |
| Leukocyte growth factors | Pegfilgrastim | Decrease the incidence of febrile neutropenia in subjects treated with chemotherapy | Pegfilgrastim-apgf | June, 2020 |
| | | | Pegfilgrastim-bmez | November, 2019 |
| | | | Pegfilgrastim-cbqv | November, 2018 |
| | | | Pegfilgrastim-jmdb | June, 2018 |
| | | | Pegfilgrastim-pbbk | May, 2022 |
| | Filgrastim | Decrease the incidence of febrile neutropenia in subjects treated with chemotherapy | Filgrastim-aafi | July, 2018 |
| | | | Filgrastim-sndz | March, 2015 |
| | | | Filgrastim-ayow | February, 2022 |

(*Continued*)

**Table 1** (Continued).

| Drug Class | Reference Product | Indications | Biosimilar(s) | FDA Approval Date |
|---|---|---|---|---|
| CD20-directed cytolytic monoclonal antibody | Rituximab | Non-Hodgkin's lymphoma, granulomatosis with polyangiitis, Wegener's granulomatosis, microscopic polyangiitis, CLL | Rituximab-arrx | December, 2020 |
| | | | Rituximab-pvvr | July, 2019 |
| | | | Rituximab-abbs | November, 2018 |
| Long-acting human insulin analog | Insulin glargine | DM | Insulin glargine-yfgn | July, 2021 |
| | | | Insulin glargine-aglr | December, 2021 |

**Note**: Data from Padda et al[14] and FDA.[15]
**Abbreviations**: TNF, Tumor Necrosis Factor; anti-VEGFA, Anti-vascular endothelial growth factor A; nAMD, neovascular age-related macular degeneration; ESA, Erythropoiesis Stimulating Agent; CKD, Chronic Kidney Disease; HIV, Human Immunodeficiency Virus; HER2, Human epidermal growth factor receptor 2; CLL, Chronic Lymphocytic Leukemia; DM, Diabetes Mellitus.

highly comprehensive and sensitive to detect any difference in the drug structure, mechanism of action, or other product characteristics between the biosimilar and the original biologic product, then the preclinical studies to assess the pharmacokinetics, pharmacodynamics, immunogenicity, and toxicity which are essential for the approval of both FDA and EMA, followed by the clinical studies which are critical to verify the equivalence in the bioavailability, efficacy, and safety of the biosimilar with the original biologic product. Also, it will demonstrate that there are no differences in the pharmacodynamics, immunogenicity, and safety measures[9,10] (Figure 1).

Although FDA and EMA perspectives may differ in their requirements, both necessitate a minimum of one clinical trial to compare the immunogenicity of the biosimilar and the original biologic product recommending head-to-head comparison.[9,11,17] The biosimilar drug does not require many clinical studies, unlike the original biologic product that needs a long series of consecutive clinical trials, especially in Phase III with a clear study design protocol to prove the efficacy and safety.[9,17] The type and frequency of immunological responses, including any serious or severe clinical reactions that may occur to the patient, should also be considered throughout the comparison.[16] The bioequivalence trial designs are necessary to demonstrate the biosimilarity between the biosimilar agent and the original reference product. They are strongly alike (ie, no clinical difference between them). Nevertheless, the non-inferiority trials are also

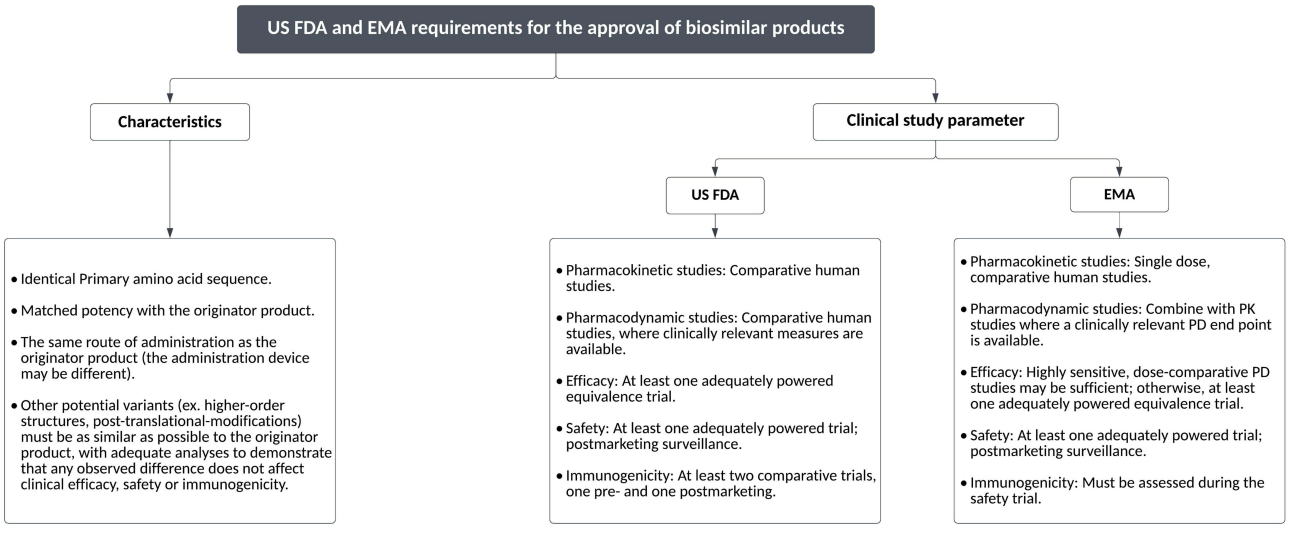


**Figure 1** Requirements of the US FDA and EMA for the approval of biosimilar products.
**Note**: Data from Verrill et al.[1]
**Abbreviations**: US FDA, United States Food and Drug Administration; EMA, European Medicines Agency.

agreeable and convenient in some conditions,[9,12] taking into consideration that the equivalence and non-inferiority trial designs should have margins that must be accurately measured in reference to accepted clinical variations bearing in mind the previous variation that already exists in the original reference product superiority trials. In the two previous clinical study designs, the statistical significance is usually measured using the confidence intervals (two-sided for equivalence and one-sided for non-inferiority trials).[18]

The FDA recommendations are to calculate the appropriate sample size and select a sufficient study population to identify the important clinical differences between the biosimilar agent and the original biologic product. They are also used to demonstrate pharmacodynamics, pharmacokinetics, immunogenicity differences, or any other factors concerning safety signals reaching the point of totally equivalent evidence-based. Therefore, the regulatory approval of a biosimilar agent is provided only if all the clinical measures are totally equivalent evidence-based through the development process of the biosimilar clinical trials indicating that they are the same without any clinical dissimilarities with the original reference product.[16]

Extrapolation, which enables to license for other indications of a biosimilar approved before for the original biologic product without any need for additional clinical studies, should be considered. When reaching the point of totally equivalent on an evidence-based and all the satisfactory pieces of evidence provided regarding the original biologic product mechanism of action in each indication and the biosimilarity evidence between both the biosimilar and the original biologic product in any related in vitro functional tests, then the extrapolation is allowed[9,19,20] (Figure 2). For instance, trastuzumab is the first biosimilar (Ontruzant®) that has gotten approval in the treatment of the early stages of breast cancer combined with chemotherapy depending on its similarities with the original biologic product, which permitted to get approval in other indications like metastatic breast cancer and metastatic gastric cancer as well.[1,21,22]

## Science Behind Manufacturing

As for biologics, either originator or biosimilar, the manufacturing process is the most important factor that ensures product quality and consistency. This is owing to their complexity and intrinsic heterogeneity, and thus, it is practically impossible to describe each molecular variant of these complex products completely. Under these circumstances, manufacturing companies must maintain a consistent production process over time to ensure that the final product meets the desired quality and consistency criteria.[1] The key starting move is to set up a perfect cell line on a small scale (such as volumes in milliliters) with a finite number of cells. However, when considering the production of biologics on

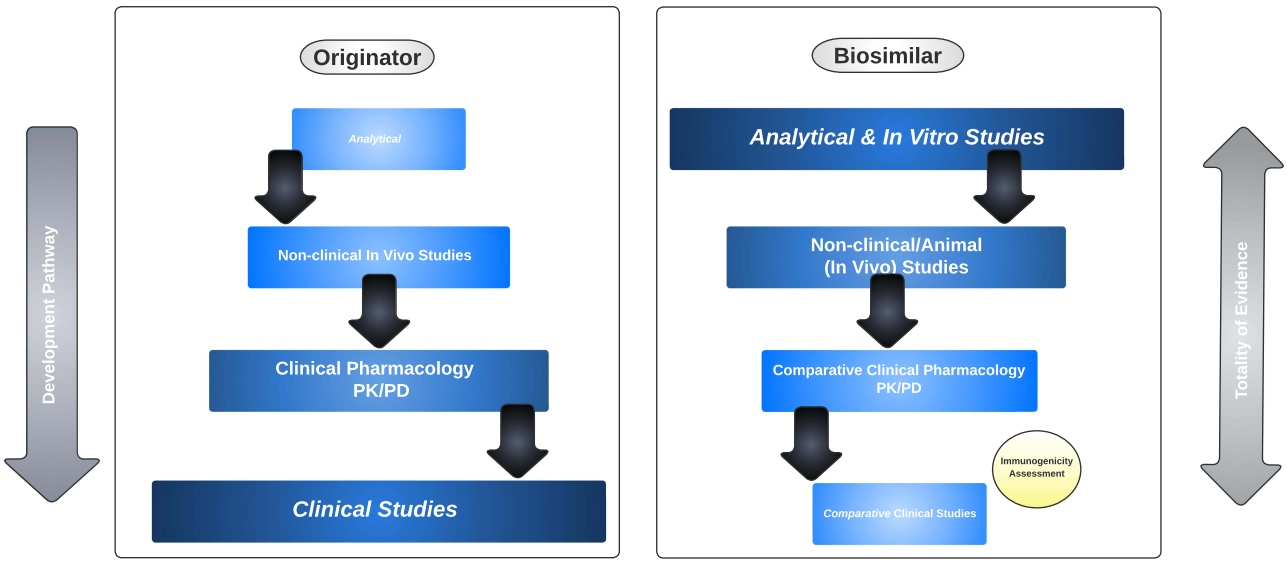


**Figure 2** The totality of evidence for biologics and biosimilars.
**Note**: Data from Verrill et al[1] and Ogura et al.[4]
**Abbreviation**: PK/PD, pharmacokinetics/pharmacodynamics.

a commercial scale, the cells multiply through numerous sequential rounds, after which they will be cultured in huge bioreactors (ie, volumes in thousands of liters). Then, the biologic product has to be purified using different techniques such as filtration and chromatographic procedures.[23] Finally, across all the steps, intensive and strict testing should be applied (ie, starting from cell bank development up to the final batch assessment).[1,3]

It is noteworthy to mention that even in the same batch, there will inevitably be various forms of the protein, which applies to all biologics, whether originator or biosimilar. These different protein forms share an identical sequence of amino acids; however, post-translational modifications may vary.[24] An example of such modification is the glycosylation pattern, ie, adding sugar molecules in different positions may take place. This can be translated to a pronounced impact on the stability, solubility, and intrinsic functional properties of the protein.[1] Other examples include acetylation, phosphorylation, and sulfation.[25] All these processes are controlled by several enzymes within the cell, which means that they can be affected by culture conditions and cell type. Additionally, the protein may undergo chemical modifications (such as oxidation) during purification and storage. In such cases, the changes depend on temperature, pH, or other external factors. Various molecular variants arise against this background, and it is infeasible to identify all of these variants explicitly, even with sensitive analytical techniques.[26] Therefore, consistency of the production process is the only guarantee for reproducibility. However, and even with originators, changes may be required occasionally. In these circumstances, it must be demonstrated that these changes would not influence product efficacy, safety, immunogenicity and rigorous quality control. Biosimilars require similar rigorous control regarding the manufacturing process as that applies to originator biologics.[7,8]

The amino acid sequence in both originator and biosimilar must be identical; however, the originator manufacturer will not reveal details about the cell line and production process even if the originator is off-patent. Accordingly, a biosimilar manufacturer will have to develop his cell line and production process by a "reverse engineer" to eventually have an adequately identical product to the originator biologic. In other words, he will have to apply similar principles that were used to develop the originator. But in whatever way, the ultimate process of manufacture will always be a bit different, and necessarily, protein microheterogeneity will occur in different manners, either within the single product or between different ones (ie, reference product and biosimilar). Therefore, understanding the extent of deviation that is considered to be acceptable in quality attributes (ie, will not affect efficacy and safety) is crucial.[1]

In this context, it is important to understand which product attributes relate to efficacy, safety, pharmacokinetics, and quality. For a biosimilar product to be approved, quality attributes which have relevance to the product function must be strongly similar to the originator product. At the same time, it is acceptable for other attributes recognized to be unassociated to function to have minor differences.[9,10] An instance of a critical attribute with monoclonal antibodies is the fucosylation in the Fc region (ie, an enzymatic addition of fucose sugars). The degree of fucosylation can have considerable consequences on antibody-dependent cell cytotoxicity (ADCC). Greater ADCC is commonly observed with afucosylated antibodies, which may be translated into significant clinical consequences.[27] In an animal model of breast cancer, median progression-free survival has increased by two folds as a consequence of fucosylation of trastuzumab compared with the conventional molecule. Therefore, the degree of fucosylation must be rigorously controlled in both products (ie, originator and biosimilar).[28]

In more general terms, substantiation of analytical similarity and comprehensive characterization is the foundation for proofing biosimilarity.[9,12] Essential characteristic requirements by both the FDA and the EMA for biosimilars approval include an identical sequence of primary amino acids, potency to be matched between the products, and the same route of administration. Other requirements include that post-translational modification, higher-order structures, and other potential variants are to be as similar as possible. Other clinical parameter requirements include pharmacokinetics and pharmacodynamics studies, efficacy, safety, and immunogenicity trials.[29] After that, an approved biosimilar can be prescribed without a doubt about its quality. Nevertheless, it should be noted that the analytical properties of various biosimilars are evaluated versus the originator product, not against another biosimilar. Hence, for any critical quality attribute, a range of values arises that must overlap significantly with the reference product. In virtue of these facts, prescribing a biosimilar should be in line with the brand name, and switching between brands should be minimized.[1]

In nonmedical switching, for the reason that is not medically necessary – usually to save money, the switch may be initiated by the insurance company (or whoever pays for the drug) to move to a cheaper option. On the other hand,

patients themselves may decide to switch because their copayment may be eliminated or much less with the other drug. The physician also could originate the switch in an attempt to decrease costs. The essence of a biosimilar is that the drug is highly similar to the originator product without any clinically meaningful differences in the drug's safety profile, purity, and potency. Thus, if the patient experiences a medical problem with either the originator drug or the biosimilar, simply switching from one to the other would not help, as they are essentially just different versions of the same drug (ie the patient would need to switch to a completely different drug).[30]

## Promoting Patient Access to Innovative Treatments

By introducing new biosimilar products, direct cost savings have been accomplished either by decreased list price compared to the originator or even by provoking reductions in the reference product price and competitor biosimilars; all these matters have opened the door for increased patient access to biologics.[16] This is to say that the introduction of biosimilars triggers a fall in the overall cost of biological therapies.[31] Consequently, this diminished pricing will unleash scarce health resources and preserve the quality of care, which will positively affect healthcare sustainability. As a case in point, published microeconomic data from a Spanish public hospital revealed that treatment expenditures for a patient with Crohn's disease were lowered by almost two-thirds (around 61% reduction) after two years of infliximab-bearing biosimilar acquisition.[2] In light of macroeconomic data, savings of EUR 15 billion were projected between 2015 and 2020 across Europe.[31] This cost-effectiveness has a paramount impact that -with certainty- gives rise to better allocation of healthcare resources and budgetary redistribution and eventually improves patient access to biological treatments.[32] Over and above, these savings and reallocated funds can be invested to acquire new healthcare technologies and services and also, to pave the way to start biological treatment at earlier stages whenever it is needed.[2]

The capacity to penetrate the market at a decreased list price is a principle engine for developing a biosimilar product, even if the subsequent biosimilar uptake differs between countries.[33] However, anticipatory rises in originator price that precede the launch of a biosimilar may restrain the cost savings as a whole.[34] Moreover, competitive price reductions offered by manufacturers of the originator product may reduce the return on investment for the biosimilar.[16] As an example, cost savings in the USA attributed to biosimilar filgrastim were lower than what was anticipated.[35] Likewise, and even though FDA/EMA approval of many biosimilar products, revenue from the epoetin alfa originator persists to be high.[16] Finally, it is worth noting that in the USA, unlike in the EU, reduced price competition may be due to the scarcity of biosimilar competitors along with the dominance of biological manufacturers developing biosimilars.[36,37]

## Benefits Beyond Price

Benefits from biosimilars may broaden beyond direct cost savings, which could be deemed particularly in the case of cancer treatments. In certain instances, an increased uptake can be seen with many combination biological therapies, including combinations of the approved biosimilar with the originator product. In other words, innovation to develop novel treatment strategies that use currently available products to optimize treatment is considered the backbone of therapy for numerous cancer types.[16]

Other benefits of biosimilars that transcend price aspects include the inclusive analysis done by manufacturers of biosimilars to reference products. This comprehensive analysis (structural and functional) of reference products in different patches has enhanced the knowledge and understanding of originator biologics properties.[38] Moreover, the introduction of different biosimilar products has mitigated the risk of drug shortages -a serious consideration of healthcare authorities- due to the availability of more than one version in the market. Another important aspect is that manufacturers of originator products may pursue innovation of new molecules or improve existing ones. These ceaseless moves are triggered by the perception of being commercially threatened by the introduction of biosimilars. On the other hand, biosimilars manufacturers will aim to offer privileges such as less immunogenicity, higher stability, or easier delivery modes.[2]

## Opportunities of Biosimilars in the Middle East and Africa (MEA) Region

The MEA market shows a notable rise in biologics' value share over recent years, which aligns with the global market trends. From 2015 to 2019, biologics' value share in the MEA region was estimated to reach almost 4.1 billion USD, with a 14.5% annual growth rate. The Kingdom of Saudi Arabia (KSA) is the market leader (with over 1.8 billion USD sales), followed by the United Arab Emirates (UAE), Egypt, and Algeria, with almost 450 million USD each.[39] Moreover, the MEA biosimilars market is forecasted to grow at a Compound Annual Growth Rate (CAGR) of 24.96% from 2021 to 2026. Rises in healthcare expenditures, Gross Domestic Product (GDP), and the demand for cost-effective treatments; all resulted in this projected market growth.[40]

In Tunisia, the first edition of biosimilars guideline was published in July 2018 by the "Direction de la Pharmacie et du Medicament" (DPM).[41] This guideline referred to world health organization (WHO), EMA, International Council for Harmonisation (ICH), and benchmarked with the Egyptian and Jordanian guidance. This guideline indicates that once the quality comparability to the Reference Medicinal Product (RMP) is proven, preclinical and clinical studies can be pursued.[42] The guideline did not require specific analytic tests; however, it invites the applicant to refer to EMA and ICH guidelines for more details. All pharmaceutical companies are called to renew their applications for EMA every five years.[41] Interchangeability is assessed case by case. However, physicians in public health centers are limited by hospital tenders.[43] The Central Pharmacy of Tunisia, a Ministry of Health (MOH) affiliate, is the unique payer of imported medicines. The monopoly of purchasing enabled the MOH to ensure the stability of prices and to absorb the inflation rate.[44] Moreover, it strengthens the negotiation power and reduces the margin gain of secondary payers and distributors. To implement a long-term cost-saving strategy, the MOH started a health technology assessment program, which reflects the government's incentive to improve the quality of local biosimilars.[41]

In Egypt, regulations for the registration of biological products have been implemented since 2009 through the Minister decree 297/2009, adopting guidelines for submission of registration dossier based on full data (quality, preclinical and clinical data). A Guideline for Registration of Biosimilar Products in Egypt was issued in 2014 and has been published and implemented since then. In 2020, the Egyptian Drug Authority (EDA) published its latest guideline for the registration of biosimilar products, including all requirements for the comparability exercise as referred to ICH, WHO, EMA, and the FDA. Registration of a biosimilar product should follow one of two approaches; imported or locally manufactured products. Clear principles for the development of biosimilar products have been stated, such as; the rationale for the choice of the reference product should be provided in the submission, and a comprehensive understanding of all steps in the manufacturing process for the proposed product should be established during product development. A stepwise approach is recommended throughout the biosimilar product development program. Quality aspects include analytical consideration, specifications (release of drug substance/drug product), references standard, and final formulation.[45] External reference pricing is the policy adopted in Egypt.[46] The Unified Procurement Authority (UPA) in Egypt is the centralized procurement and supply interface that aims to ensure equitable access to medicinal and health technology products through conducting evidence-based technology assessment, strategic value-driven procurement methods, establishing a robust and sustainable supply chain, and enabling efficient utilization of resources.

However, most healthcare systems in the MEA region are price-conscious, and reimbursement decisions are shaped mainly by drug prices and clinical outcomes. The economic turmoil in this region (which is relayed to oil prices) exerts further pressure on healthcare systems, which imposes several worries about their spending capacity compared to developed markets. Countries in this region have varying economies, some can modify their healthcare expenditure, but others are struggling. Other challenges in the region are; the complexity of the manufacturing process, high cost, availability of other generic drugs with lower prices, high prevalence of certain diseases such as diabetes, and increasing cancer-related mortality rates. Lenient government regulations, together with government support and initiatives, should provide major openings in this market.[39,40] Interestingly, the majority of the MEA region countries have a well-defined regulatory landscape for biosimilars (Tables 2 and 3).

**Table 2** Countries in MEA Region and Their International Reference Bodies

| Country | International Reference Body |
|---|---|
| KSA | EMA, FDA |
| UAE | EMA, WHO |
| Egypt | EMA, WHO, FDA |
| Jordan | EMA |
| Lebanon | EMA, FDA |
| Algeria | EMA, FDA |
| South Africa | EMA, FDA |
| Tunisia | EMA |

**Note**: Data from Nathalie et al.[39]
**Abbreviations**: EMA, European Medicines Agency; FDA, Food and Drug Administration; MEA, Middle East and Africa; UAE, United Arab Emirates; WHO, World Health Organization.

**Table 3** Different Regulations of Biosimilars Pricing in Countries of the MEA Region

| Country | Regulations of Biosimilars Pricing* |
|---|---|
| UAE | The Ministry of Health and Prevention (MOHAP) recently published guidelines for biosimilars pricing with different options such as; having 70% of the originator's CIF price before any reductions or having the ex-factory price in the country of origin, amongst other options. |
| Egypt | The Ministry of Health (MOH) in Egypt amounts 35% reduction for the first 5 biosimilars prices below the corresponding originators, and subsequent biosimilar products are priced at a 40% reduction. |
| South Africa | The price is based on a Single Exit Price (SEP) which should be agreed upon between the Pricing Committee of the Department of Health and the applicant. |
| Lebanon, Tunisia, Kuwait | There are no specific guidelines for biosimilar pricing (ie, it follows pricing for generic products). |

**Notes**: Data from Nathalie et al[39] *Generally, the difference in pricing between originator products and biosimilars extends from 10% in Morocco and Saudi Arabia, up to 20% in Jordan, 30% in Algeria, and up to 40% in Egypt. CIF price: the cost, insurance, and freight price.
**Abbreviations**: MEA, Middle East and Africa; UAE, United Arab Emirates.

## Conclusion

Biosimilar products will play a momentous part in the treatment journey of patients with serious ailments. Along with marked decreases in associated expenditures, biosimilars will potentially improve patient access to healthcare, upgrade the quality of care, and enable more patients to reach optimal treatment. The MEA market shows a notable rise in biologics' value share over recent years; however, constraints to increase biosimilars uptake should be addressed. To demonstrate efficacy, safety, and quality in local settings, more stringent biosimilars guidelines, real-world data incentives, and local clinical studies should be established. Also, engaging the local stakeholders in clinical monitoring, raising the awareness among health care practitioners (HCPs) about biosimilars, combining pricing systems to offer a preferential and competitive environment, and fostering agreements and partnerships with recognized biotech industries will help to improve the patients and HCPs' acceptance, offer a preferential and competitive environment, and permit the transfer of the technology and the knowledge. All of these promising strategies can provide major openings in this market and provide better opportunities for the patients.

## Abbreviations

US FDA, United States Food and Drug Administration; EMA, European Medicines Agency; EU, European Union; USA, United States of America; ADCC, Antibody-dependent cell cytotoxicity; MEA, Middle East and Africa; KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates; CARG, Compound Annual Growth Rate; GDP, Gross Domestic Product; DPM, Direction de la Pharmacie et du Medicament; WHO, world health organization; ICH, International Council for

Harmonisation; RMP, Reference Medicinal Product; MOH, Ministry of Health; EDA, Egyptian Drug Authority; UPA, Unified Procurement Authority; HCPs, health care practitioners.

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