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Current Status of Biosimilar Regulations in the MENA Region

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Abstract

This review article explores the regulatory situation of biosimilar registration pathways in the Middle East and North Africa (MENA). With most countries in the world have either adopted official regulatory guidelines for biosimilar approval or are in the process of developing such guidelines, countries in the MENA region are advised to accelerate the process of adopting pathways for biosimilar approval primarily for preventing the entry of intended copies into such markets and risking patients' safety in addition to jeopardizing clinical outcomes of the different disease modalities that are treated by biologics. Additionally, biosimilars are playing a significant role in reducing the significant public expenditure on biological therapy and thus increasing the accessibility of these medications to a larger population of patients. The article details the countries in the MENA region that have adopted official and scientific guidelines for biosimilar approval pathways. The article also draws a comparison between different countries on issues such as comparability studies, extrapolation of indications, interchangeability and non-clinical quality requirements. In conclusion, only four countries out of the 15 countries they comprise the MENA region have adopted clear regulatory pathways for biosimilar registration and approval. This situation should be of urgent importance to policymakers responsible for public health bodies in countries that lack such guidelines due to the negative consequences that could result due to the absence of clear biosimilar regulations.

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INTRODUCTION

The introduction of biological medicinal products in the early '80s has revolutionized the treatment of several disease modalities including cancer, autoimmune diseases and hormonal deficiencies (Moroder and Musiol, 2017; Balagué *et al.*, 2009; Oldham, 1984). Unlike their chemical medicinal counterparts, biological products are synthesized based on recombinant DNA technology and in living organisms such as bacteria, yeast and mammalian cells (Reichert and Paquette, 2003). The resultant protein products are of high structural complexity when compared with their classical chemical counterparts due to the three-dimensional topology of proteins when synthesized within biological systems and the several variables influencing the manufacturing process of each biological entity (Reichert and Paquette, 2003). This complexity in structure has resulted in the difficulty of establishing a fast track generic industry for

these molecules by the pharmaceutical industry as there were no technical and regulatory pathways to create such generic products and introduce them into markets (Sekhon and Saluja, 2011). However, and due to the enormous profitability of biological molecules and the fact that several of them lost their patent exclusivity, several pharmaceutical companies embarked on developing generic products of biologicals to compete with their originator counterparts and to seize the vast economic opportunity in pursuit of gaining marketing authorization to introduce these generic bioreplicas into the market (Blackstone *et al.*, 2013). The term biosimilar was introduced to describe any copy of the originator branded biological molecule, which could demonstrate high comparability to the originator in a highly rigorous clinical and non-clinical comparability exercise (Kuhlmann and Covic, 2006).

Additionally, the high cost of originator biologics and the entry of several agents of these into the clinic created huge financial pressure on the public health sector of several countries that offer full coverage public health insurance for their citizens (Blackstone and Fuhr, 2007), this in turn, incited several regulatory bodies within different countries to develop guidelines for biosimilar approval and registration to reduce public expenditure and expand the therapeutic options available to the public (Gottlieb, 2008). The first regulatory entities that were eager to adopt and accelerate the development of such guidelines were members of the European Union as all these countries adopt full health insurance coverage to their citizens. The establishment of a biosimilar registration pathway would ensure cutting public expenditure while conserving the quality and robustness of the health outcomes that are related to originator biologics (Haustein, 2012). Accordingly, the first guidelines for the registration pathway of biosimilar drugs were developed by the European Medicines Agency [EMA] in 2005 which was followed in 2006 by the regulatory approval of the first biosimilar in Europe Omnitrope® [A biosimilar recombinant growth hormone] by Sandoz Pharmaceuticals in Austria (Schiestl *et al.*, 2017). Since then, more than 20 biosimilars have been approved, and over 11 applications are being reviewed by the agency (GaBI, 2020). The development of a regulatory pathway for biosimilar approval in the European Union has also been followed by the development and creation of regulatory pathways for biosimilar approval in most developed regions including North America, Latin America and Asia (Tsai, 2017; Garcia and Araujo, 2016; Dougherty *et al.*, 2018). In the Middle East and North Africa, the regulatory pathways for regulatory approval are still variable between different countries with some having no regulatory path at all for biosimilar drugs and other with no specific guidelines and thus allowing the approval and registration of intended copies or biomemics as generic medications and thus compromising the quality of these medications and exposing the patients to significant safety issues. Most of the countries that have standardized regulatory pathways for biosimilar approval such as Jordan, Saudi Arabia, Lebanon and Egypt have adopted international standards for the comparability exercise of a biosimilar versus its originator biological such as the EMA, FDA and WHO guidelines (ali "Malkawi" *et al.*, 2018; Gabi, 2020). However, there remain several countries with no standardized guidelines whatsoever such as Libya, Morocco, Tunisia, Algeria, Yemen, Syria, Iraq and the Gulf countries. This review aims to focus on two major issues regarding the regulatory situation in the MENA region, the first is to differentiate between countries that have scientific and rigorous guidelines for biosimilar approval from those who do not and the second is to highlight and draw a comparison between the standardized pathways which have adopted these guidelines in four main issues and these include: comparability studies, extrapolation of indication, interchangeability and Non-clinical quality attributes of biosimilars.

Comparability Studies

According to the EMA guidelines and for regulatory approval, comparing a biosimilar with a publically available standard such as a pharmacopeial monograph is not sufficient for the demonstration of comparability with the reference product. (Lee *et al.*, 2012). A biosimilar has to prove a high level of similarity with the reference product in an extensive comparability exercise with regards to quality, safety and efficacy. This requires the biosimilar manufacturers to produce preclinical, clinical and immunogenicity studies to confirm sufficient similarity with the originator biologic. Un-abiding to these guidelines or not setting any guidelines such as the ones adopted by the EMA will risk the possibility of having a "biomimic" or an intended copy to obtain a registration pathway for a molecule that is treated from a regulatory point of view as a generic and consequently exposing the patients to either an inferior molecule or a molecule with serious safety risks (Ghia *et al.*, 2015). In the MENA region, only four countries have clear guidelines for manufacturers to produce comparability studies when submitting their registration dossier. These countries include Jordan, Saudi Arabia, Egypt and Lebanon. The most stringent and detailed guidelines in terms of the comparability exercise are the Jordanian and

Table 1: Comparative summary between biosimilar regulatory pathways worldwide andthe MENA region.

	EMA	Jordan	Saudi Arabia	Egypt	Lebanon
Comparability Studies	Comprehensive head-to-head comparison of the biosimilar with the reference medicine to show high similarity in chemical structure, biological function, efficacy, safety and immunogenicity.	Comparative quality, non-clinical and clinical studies are needed to substantiate the similarity of structure/composition, quality, efficacy and safety, immunogenicity.	Side-by-side comparative studies unless otherwise justified	Head-to-head comparison to establish similarity in quality, safety, and efficacy. complete comparability quality exercise	Head-to-head comparison of a biotherapeutic product with a licensed originator product with the goal to establish similarity in quality, safety, and efficacy.
Extrapolation of Indications	Allows extrapolation of therapeutic indication, safety and efficacy data (fewer clinical trials or no trials at all need). supported by scientific evidence generated in robust comparability studies (quality, non-clinical and clinical).	Extrapolation from one therapeutic indication to another is appropriate where: the mechanism of action and the receptor are known to be the same as the condition(s) for which similarity in efficacy has been established	No clear guidelines regarding extrapolation of indications is mentioned.	Extrapolation of indication could be possible if all the following conditions are met: A sensitive population criterion that is able to detect potential differences between the biosimilar and reference product is used. The clinically relevant mechanism of action.	If similar efficacy and safety of have been demonstrated for a particular clinical indication, extrapolation of these data to other indications of the reference may be possible if all of the following conditions are fulfilled: A sensitive clinical test model has been used, The clinically relevant mechanism of action. Safety and immunogenicity have been sufficiently characterized. If the efficacy trial used a non-inferiority study.

Table 2: Comparative summary between biosimilar regulatory pathways worldwide andthe MENA region.

	EMA	Jordan	Saudi Arabia	Egypt	Lebanon
Interchangeability &	EMA guidelines state the decision is taken at the national level.	The decision of interchangeability should be taken following the opinion of a qualified health professional.	No Guidelines available	No Guidelines available	Automatic substitution at Pharmacy level is not allowed and interchangeability should be the decision of the Healthcare Professionals only.
Non-Clinical Requirements	Comparative in vitro studies: (Binding to target(s)) should be included. in vivo animal study is usually not considered necessary.	Comparative in vitro and in vivo (animal) studies should be designed. - At least one repeat-dose toxicity study, including toxicokinetic measurements, should be conducted in relevant species	The regulatory details regarding non-clinical requirements are not explained in detail.	Comparative in vitro and in vivo (animal) studies should be designed.	The regulatory details regarding non-clinical requirements are not explained in detail. Manufacturer should provide data regarding the Pharmacology, pharmacodynamics and Toxicology

Egyptian guidelines which clearly state that both clinical and non-clinical studies between the originator and the biosimilar must be included in the registration dossier. The Saudi and Lebanese guidelines state that a head to head comparability exercise must be included in the regulatory dossier of the biosimilar but lack details of the clinical requirements of the biosimilar. Figure 1 represents a map detailing the regulatory status of biosimilars in the MENA region. As most of the MENA countries still lack regulatory pathways for the identification of a biosimilar drug and either adopt standard generic pathways for marketing authorization for biosimilars or lack none. This situation creates a significant health issue for the population of these countries as several "intended copies" could be used for the treatment of serious diseases and consequently jeopardizing the health and safety of patients. Local health authorities in these countries should fast forward the process of introducing proper legislation to create legal pathways for biosimilar registration to protect patients and achieve maximal health benefit outcomes.

Extrapolation of Indications

The extrapolation of indications for biosimilars remains somehow controversial among regulatory authorities. Extrapolation of indications for a follow-up biosimilar from one indication to all indications of the reference biological product is possible as long as the biosimilar meets specific safety and efficacy criteria provided in the tested evidence (Weise *et al.*, 2014). The EMA guidelines set specific standards for indication extrapolation, and these include

(1) a sensitive clinical model to predict the potential differences between the biosimilar and its reference product;

(2) The mechanism of action regarding the target receptor should be identical;

(3) Safety and immunogenicity data of the biosimilar have been extensively characterized (Reinisch *et al.*, 2015).

In the MENA region, The Egyptian and Lebanese

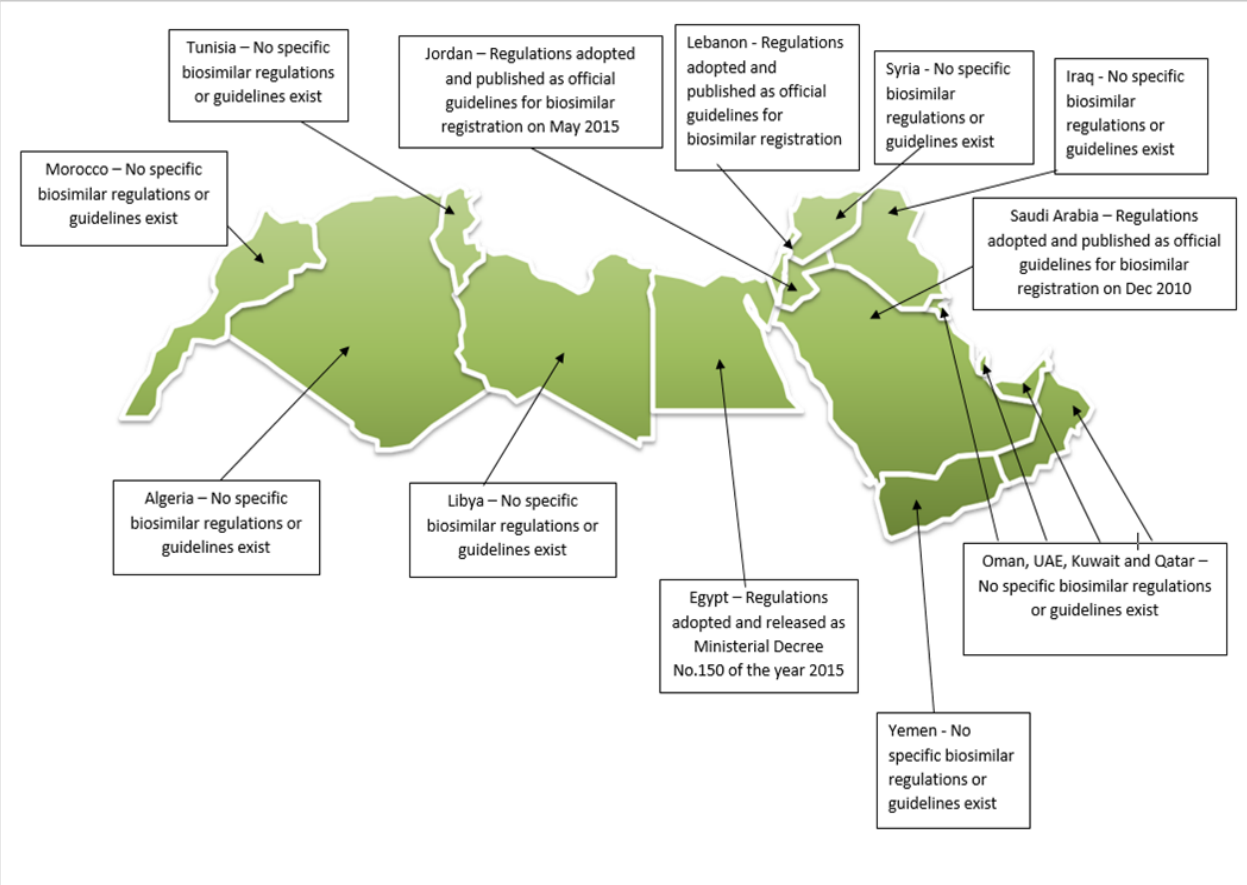

Figure 1: Regulatory situation of Biosimilars in the MENA region

guidelines provide a clear set of criteria for biosimilar extrapolation of indications which is mainly based on the EMA guidelines. The Jordanian guidelines allow for extrapolation and mention that receptor identity is crucial for the extrapolation exercise but do not target the clinical sensitivity models outlined in the EMA and WHO guidelines. The Saudi biosimilar guidelines allow extrapolation but do not set detailed criteria for the manufacturers regarding the requirements and scientific requirements to allow biosimilar extrapolation and leave the issue for a case by case regulatory decision.

Table 1 includes a comparative summary of all regulatory aspects of biosimilar approval according to EMA, WHO and the MENA countries.

Interchangeability and Automatic Substitution

International regulatory authorities vaguely address the subject of biosimilar interchangeability and automatic substitution, and this has serious consequences, specifically in countries where the government supplies medications on a tender, based or national procurement process. The EMA has no guidelines on interchangeability and leaves the decision and advice to the drug regulatory authorities within the European Union. The WHO guidelines are similar to EMA's as the decision is left to be regulated by national authorities. In the MENA region, Both Jordanian and Egyptian guidelines clearly state the automatic substitution at the Pharmacy level is not allowed, and switching is the sole responsibility of the treating health professional. The Saudi and Lebanese guidelines do not mention any guidelines whatsoever regarding interchangeability or automatic substitution. This situation is more complicated by the fact that interchangeability is being performed on a national level in most MENA countries within the Public health sector as drug procurement is tender based and depends on the generic name of the molecule which leads to the introduction of the biosimilar automatically and leaves no alternatives to health professionals for any clinical decisions regarding biosimilar substitution or interchangeability. This situation requires international and national health authorities to clarify the concept of the governmental bodies responsible for biological drugs procurement.

Non-Clinical Requirements

The most detailed regulatory guidelines regarding biosimilar registration concern the non-clinical

quality part of the registration dossier.

According to EMA guidelines, any biosimilar must perform a complete comparative in vitro studies that include:

(1) Pharmacology;

(2) Pharmacodynamics;

(3) Pharmacokinetic;

(4) Toxicology; and Immunogenic studies. All MENA countries specify the need for all studies mentioned above.

Additionally, EMA regulations state that in vivo studies are not considered necessary, but the Jordanian and the Egyptian guidelines require the performance of animal studies in vivo studies to confirm the pharmacological, toxicological and immunogenic data regarding the quality of the biosimilar.

CONCLUSIONS

The governmental regulations of biosimilar marketing authorization based on scientific and clinically rigorous data is needed to ensure patient safety and drug efficacy. The lack of such rules or the absence of precise regulatory pathways for biosimilar assessment and evaluation allows the entry of intended copies of the originator biological molecules and consequently threatening the patients' safety and optimal health treatment outcomes. Additionally, the complete absence of biosimilar guidelines or marketing authorization pathways of biosimilars will reduce patients' accessibility to biological therapy as these medications are significantly costly and could represent a financial burden. Biosimilars are the reduced cost of an average of 30 % when compared to originator biologicals. This article reviews the countries that have adopted such regulations in the MENA region and benchmarks these regulations against EMA guidelines. Only four countries out of the 15 countries that comprise the MENA region have adopted clear regulatory pathways for biosimilar registration and approval. This constitutes a serious issue as most countries worldwide have either adopted such guidelines or are in the process of regulating biosimilars. To ensure patient safety and treatment efficacy, regulatory bodies in the MENA region should develop these guidelines either with the cooperation of international health authorities such as the WHO or other special expert committees from neighbouring countries.

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Conflict of interest

None

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