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Pharmacovigilance of Biosimilars in Yemen: Challenges in Poor-Resource Setting

Mohammed A. Alshakka [1], Wafa F. Badulla[2], Sara A. Alshagga[3], Adel H. Aldhubhani [4], Nazeh M. Al-Abd[5], Mohamed I. Ibrahim[6]

Abstract

Biosimilars are biological medications that are very analogous to confirmed pose biologics and have been approved for use in patients in certain countries worldwide. These biological materials have definite features, which have further challenges in pharmacovigilance. Nevertheless, the evaluation of efficacy, safety, and post-marketing investigation are fundamentals to recognize, estimate and avoid side effects of chemically synthesized small molecule drugs and biologicals, because the complete safety outline could only be recognized after post-marketing.

In this article, the researchers have tried to provide background about biosimilar pharmacovigilance and have discussed the implications for biosimilar pharmacovigilance in Yemen. Moreover, this article reviews several aspects of biosimilar pharmacovigilance, including traceability, pharmacovigilance system development and highlights some challenges in Biosimilars pharmacovigilance. The availability of biosimilars as lower-cost biologics must wisely consider issues of safety, efficacy, and traceability. Strict pharmacovigilance procedures are needed to evaluate the potential variances in safety indications between biosimilars and their reference products and recognize the adverse drug reactions with biologics and biosimilar products. Pharmacovigilance of biologicals should contain procedures that are straightforwardly used by prescribing practitioners to guarantee that data are reliable and new safety signals are appropriately reported and allocated to the precise and accurate product.

Keywords: Biosimilars, Pharmacovigilance, Safety, Efficacy, Traceability.

[1]Clinical Pharmacy Department, Faculty of Pharmacy, University of Aden, Republic of Yemen.
[2]Pharmaceutical Chemistry Department, Faculty of Pharmacy, University of Aden, Republic of Yemen.
[3]Almarfady Dental Centre, Almansorah, Aden, Republic of Yemen.
[4]Ministry of Public Health, Sanaa, Republic of Yemen.
[5]Para - clinic Department, Faculty of Medicine and Health Sciences, University of Aden, Republic of Yemen.
[6]Clinical Pharmacy and Practice Department, College of Pharmacy, QU Health, Qatar University, Doha.
Corresponding Author: Mohammed A. Alshakka **Email:** alshakka400@gmail.com

التيقظ الدوائي للبدائل الحيوية في اليمن: التحديات في وضع شحيح الموارد

محمد أحمد الشقاع[1]، وفاء فاروق بادله[2]، سارة أبوبكر الشقاع[3]، عادل حمود الذبحاني[4]، نزيه محمد العبد[5]، محمد إزهام إبراهيم[6]

ملخص الدراسة

البدائل الحيوية هي أدوية بيولوجية مشابهة جدًا للبيولوجيا المؤكدة وقد تمت الموافقة عليها للاستخدام في المرضى في بعض البلدان في جميع أنحاء العالم. هذه المواد البيولوجية لها سمات محددة، والتي لديها المزيد من التحديات في التيقظ الدوائي. ومع ذلك، فإن تقييم الفعالية والأمان والتحقيق في مرحلة ما بعد التسويق هي أساسيات للتعرف على الآثار الجانبية للأدوية الجزيئية الصغيرة والمواد البيولوجية المركبة كيميائيًا وتقديرها وتجنبها، لأنه لا يمكن التعرف على مخطط الأمان الكامل إلا بعد مرحلة ما بعد التسويق.

في هذه المقالة، حاول الباحثون تقديم معلومات أساسية حول التيقظ الدوائي للبدائل الحيوية وناقشو الآثار المترتبة على التيقظ الدوائي في البدائل الحيوية في اليمن. علاوة على ذلك، تستعرض هذه الدراسة العديد من جوانب التيقظ الدوائي للبدائل الحيوية، بما في ذلك إمكانية التتبع، وتطوير نظام التيقظ الدوائي، وتسلط الضوء على بعض التحديات في التيقظ الدوائي في البدائل الحيوية. وبالتالي، فإن توافر البدائل الحيوية كمواد بيولوجية منخفضة التكلفة يجب أن ينظر بحكمة في قضايا السلامة والفعالية وإمكانية التتبع. هناك حاجة إلى إجراءات يقظة دوائية صارمة لتقييم الفروق المحتملة في مؤشرات السلامة بين البدائل الحيوية ومنتجاتها المرجعية والتعرف على التفاعلات الدوائية الضارة مع المستحضرات الدوائية الحيوية ومنتجات البدائل الحيوية. يجب أن تحتوي التيقظ الدوائي للبيولوجيا على إجراءات يتم استخدامها بشكل مباشر من قبل الممارسين للوصفات لضمان أن البيانات موثوقة ويتم الإبلاغ عن إشارات السلامة الجديدة بشكل مناسب وتوزيعها على المنتج الصحيح والدقيق.

الكلمات المفتاحية: البدائل الحيوية، التيقظ الدوائي، السلامة، الفعالية، التتبع.

[1] قسم الصيدلة الإكلينيكية، كلية الصيدلة، جامعة عدن، الجمهورية اليمنية.
[2] قسم الكيمياء الصيدلية ـ كلية الصيدلة، جامعة عدن ـ الجمهورية اليمنية.
[3] مركز المرفدي لطب الأسنان، المنصورة، عدن، الجمهورية اليمنية.
[4] وزارة الصحة العامة، صنعاء، الجمهورية اليمنية.
[5] قسم الباراكلينيك، كلية الطب والعلوم الصحية، جامعة عدن، الجمهورية اليمنية.
[6] قسم الصيدلة والممارسة الإكلينيكية، كلية الصيدلة، جامعة قطر، الدوحة.

Introduction

A biosimilar is a biotherapeutic, proposed to be very analogous to a previously sold reference product and accepted through a monitoring procedure. The earlier biosimilar was approved several decades ago so the development of the biosimilar drug has been transformed. The monitoring perceptions have changed with developing science; nevertheless, the main principles are still the same to reveal that the intended biosimilar will not have any clinically significant transformations in terms of its safety and efficacy, in comparison with the reference product. Biosimilars have acquired acceptance since their marketing in 2006 and it is predictable to reduce healthcare costs in a similar way to small-molecule generics. However, the nature of biological drugs unlike generics (chemically similar to the reference brand product), these drugs cannot and will not be molecularly similar to the formerly produced biologically. For a product to be approved and regulated, it must meet three main principles. As the European Medicines Agency guideline [1], for the product must be a biologic, it must likewise encompass a form of the active substance of the reference product. Lastly, it must represent very identical quality features, biological action, and safety and efficacy characteristics to their reference product. Despite semantic differences, descriptions from numerous regulatory agencies, involving the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), Japan's Pharmaceutical and Medical Devices Agency (PMDA), and Brazil's Agência Nacional de Vigilância Sanitária (ANVISA) revealed concepts of bio similarity are similar worldwide and work within the three outlined tenets mentioned above. For example, the EMA definition of a biosimilar is similar to ANVISA's and PMDA's definitions. In the EMA, a biosimilar is defined as a therapeutic product that comprises a form of the active substance of a previously approved reference biological therapeutic product in the European Economic Area (EEA). The resemblance to the reference therapeutic product in relation to quality properties, biological activity, safety, and efficacy built on an inclusive similarity exercise requires to be established [2].

A biosimilar is not a precise replica of other biological. All organic products have some natural variability. It is not possible to make an exact copy of a living cell product. All organic products, including reference products, have some variations from lot to lot. A biosimilar might have a diverse structure than the original product, but the active ingredients are mainly similar in molecular and biological code. This reveals that in terms of safety or efficacy, there are no clinically significant variances between biosimilar medicine and the reference product. Only minor variances in the clinically inactive compounds are acceptable [3,4].

The World Health Organization (WHO) issued its "Guidelines for the evaluation of similar biotherapeutic products (SBPs)" in 2009. This guideline aims to offer a global standard for estimating biosimilars with a top degree of similarity with a previously approved, reference biotherapeutic drug [4-7].

The foremost biosimilar product in the U.S, Zarxio, was permitted in March 2015 and launched in September 2015 under the trade name (filgrastim-sndz). It is biosimilar to Neupogen (filgrastim), a drug that reduces the hazard of infections in patients with specific kinds of cancer taking chemotherapy which reduces total white blood cells [8]. More than 50 biosimilar products are currently under development.

(i) Estimation of efficacy and safety of drugs from the structure.

The experts were aware that structural variances between the reference and the biosimilar may have an undesirable effect on the effectiveness and safety of the biosimilar. The experts also stressed the discovery of all manufacturing steps for the biologicals because they concern about the quality of the biosimilar product. The compounds' biophysical properties could not reflect clinical efficacy and patient safety. So, giving that the structure of particular molecules is not identical, there must be proper clinical research with efficacy and safety approval for biosimilars to cross the regulatory barriers, particularly in dealings with remedial purposes where the effect of the medicine cannot be measured in a specific patient.

(ii) Justification and extent of extrapolations.

Commonly, the development programs of biosimilars are not directed through all the indications for which the authentic biological was accepted. Consequently, it is safe to extrapolate the existing clinical efficacy and safety information for the biosimilar products through identical indications as to the original ones. For monoclonal antibodies, the European Medicines Agency's (EMA guidelines) declared that interpretation of clinical efficacy and safety information to other indications of the original monoclonal antibody, although not exactly investigated throughout the clinical progress of the biosimilar monoclonal antibody, is probably built on the complete indication of comparability based on the comparability exercise and with satisfactory explanation [9].

The experts documented the difficulties related to the extrapolation of data to clinical situations not considered. Attention is necessary regarding evaluating the efficacy and safety of a biosimilar to a different degree:

a. Low problems may be occurred due to some extrapolations: e.g. epoetins, because for these compounds, the elevation in hemoglobin after administration is a pharmacodynamic marker, following the EMA guideline [9].
b. Other problems were encountered e.g. the use of G-CSF in bone marrow transplantation, stating to the World Marrow Donor Association position paper which warned about the interpretation of efficacy information from the same transplant location to that of allogeneic transplantation [10].
c. The following parts may not be appropriate to clinicians:
   - Extrapolation through different diseases: e.g., interpretation information from rheumatoid arthritis to Crohn’s disease (even if both are inflammatory diseases).

- Extrapolation through different stages of the same disease (from palliative to curative). Can, i.e. the value of biosimilar Trastuzumab in metastatic disease be extrapolated to its usage in primary breast cancer?

(iii) Pharmacovigilance of biosimilars.

Biosimilars have created an entirely new section of biotechnology manufacturing. Though, several other interests justify biosimilars need to be closely observed. The European Medicines Agency (EMA) has published an outline. Distinct importance should be cited on pharmacovigilance, considering the restricted number of patients studied through the recording course of biosimilars. Factories producing biosimilars should consequently outline a hazard-management/ pharmacovigilance strategy [11]. The aim can be accomplished by association with patient records offices that are found in numerous countries. The hazard-minimization actions for the biosimilar should be similar to the reference therapeutic product.

Facets that should be considered in the hazard-controlling/ pharmacovigilance strategy involve:

a. Safety evaluation, containing uncommon and serious side effects, are designated and anticipated, founded on the pharmacology and knowledge with the reference.
b. The strategy should guarantee that any new safety signals are monitored.
c. Exact evaluation of immunogenicity information: because immunogenic responses may appear only in a few patients, clinical information surveillance arrangements must be activated in place.
d. Distinct monitoring and identification of the drug (original or biosimilar) related to a side effect.

In October 2005 "Similar Biological Medicines" 14 biosimilar products have been permitted by the EMA for European Market. This includes the biologics of three main categories: human growth hormone, granulocyte colony-stimulating factor, and erythropoietin [12].

Taking into count the requirement for biosimilars for the USA's recent market, the FDA recently released a guideline in 2010 to try to do this to provide a licensing path for biosimilars. The guide is intended to ensure the safety, purity, and efficacy of these biosimilars before marketing. Contrasting generics for small molecules, biosimilars are is subject to rigorous regulatory processes. Several negative effects can be produced during the synthesis of these biosimilar products. Thus, in contrast to small-molecule generics, approval of biosimilars needs clinical trials to confirm that minor variations in the production of healing efficacy of the biological products. Also, pharmacovigilance permits the observation of side effects accompanying a specific one-approved biosimilar [10].

The WHO states pharmacovigilance as "science and activities related to the detection, evaluation, Understanding and preventing side effects or other drug-related side effects problem. "[13] As soon as a drug is approved by the FDA, the

drug is said to produce post-market monitoring information. Post-marketing pharmacovigilance is becoming an important situation of biosimilars as limited information is existing. Furthermore, the effect of these biosimilars on different patients concerning dose and period of treatment must be carefully controlled. For these aspects, biosimilars are required to be subject to the same pharmacovigilance guidelines as the reference product. Therefore, EMEA-approved biosimilars must present a Risk Management Plan (RMP) together with a marketing usage regular security update reports should be sent after the product has been released to the market. The RMP contains and suggests the safety outline of the drug's probable pharmacovigilance studies [14].

Ebbers *et al*, report on several pharmacovigilance activities carried out to observe the safety of these marketed biosimilars [15]. This hard work includes cohort studies and side effect monitoring studies effects of erythropoietin biosimilars, pharmacovigilance plans for safety conducted for long-term information on the use of granulocytes colony-stimulating factor, and a review of immunogenicity information for human growth hormone given to the younger patients [16].

About four out of ten biosimilars used globally are either therapeutic or adjuvant for cancer care agents. The four biosimilars that have been approved by FDA since 2015 are Erythropoietin-stimulating agents (active substance is; Epoetin-α or ζ), Growth colony-stimulating factors (active substance is; Filgrastim, Parathyroid hormones (active substance are; Teriparatide, Follitropin- α, Somatropin, Insulin glargine), and Monoclonal antibodies/fusion proteins (active substance are; Infliximab, Etanercept, and Adalimumab) from different companies. By the year 2020, the patent of these agents will be ended giving the other manufacture the chances for comparable agents to compete with their reference products which will lead to reducing the cost of the treatment [17].

As stated by the experts, the accessibility of biosimilars at a reasonable cost should be considered in terms of safety, efficacy, and traceability. The possible difference in safety indication between the biosimilars and their reference products could be accessed by applying a firm pharmacovigilance measure. The pharmacovigilance measure should cover procedures that are simply used by physicians to assure that data are reliable and new safety indications are appropriately reported and allocated to the right product [18].

Kang *et al*., stated that the WHO in 2009 established the guidelines for the regular evaluation of biosimilars, however, according to the survey carried out in 2019-2020, there are four main challenges: inaccessible/deficient reference products in the country; reduction of capitals; dilemma with the quality of some biosimilars; and problems with the practice of interchangeability and nomenclature of biosimilars [19].

In summary, pharmacovigilance is an essential aspect of biosimilars' approval because these biologics are

not small molecular genetics. Pharmacovigilance studies will carry on to be valuable for the biotech industries to provide safe and effective organic products to the market as a data pool is growing in terms of its safety outline of some of the permitted biologics.

Drug Regulation in Yemen

Generally, medicine principles and regulations are intended to confirm the quality, safety, efficacy of medicines, and accuracy of medical data. It is established, realized, observed, and re-prescribed by Medicine Regulatory Authority (MRA). The government of Yemen arranged the control of duty to the MRA. MRA is in charge of the recording of medicines; importation, circulation, and marketing of drugs; drug promotion; permitting of medicinal establishments, their workers, and performance; medicinal quality assurance; obligation to Good Manufacturing Practice (GMP) and guideline application. The Supreme Board of Drugs and Medical Appliances (SBDMA) the chief MRA in the country. It is a semi-independent organization concerned primarily with approving marketing, importation, and industrial regulation; providing certificates for drugs, medicine manufacturers, and suppliers; monitoring the drug market, and regulating the quality and pharmacovigilance of the imported drugs and therapeutic utilization [20]. A few years ago, the drug monitoring system has been sited under adequate evaluation. The SBDMA obtains capital from the government budget and holds its incomes from monitoring activities as well. However, the apparent limitation of MRA was its inability to spread a list of the recorded drugs, renewing the names of the drugs regularly to provide a reliable source about the authorized products which are officially available in the country. The Profile further revealed that there was a guide being published for the registered pharmaceuticals. Unfortunately, this guide had not been renewed for several years.

Recording and approval are principal for the community to sense ‘safe’ about using the drugs that are appropriate to their health and requirements, but the week attitude of the authority concerning sold drugs and pharmaceuticals informs have formed gaps in the Yemen healthcare system. Likewise, even though authorized supplies were existed to permit the selection of government pharmaceutical inspectors' function to review buildings in which pharmaceutical activities are accomplished. Surprisingly, local producers, private suppliers, and retail suppliers were demanded that examination visits were irregular and infrequent and an issue of concern appeared on the surface which is the contradiction between the duty of the MRA and those responsible for the pharmaceutical activities in the MOPHP [20,21].

Current Pharmacovigilance Program in Yemen

Currently, the reporting of side effects of drugs was launched in Yemen by founding a pharmacovigilance center in 2011. Currently, there are little published data about its activities, the number of reports, and how they regulate reported documents. The country and community are faced with several safety issues associated with drug smuggling, fake drugs, inappropriate and unreasonable use of drugs, importation of unessential

drugs, and medicinal errors. Consequently, it is essential to take critical steps and obvious guidelines in Yemen to guarantee patients and community safety regarding drug use.

Pharmacovigilance is a modern science concerned with detecting, understanding, evaluating, and preventing the harmful effects of drugs or any other problems related to their use. Pharmacovigilance's aim is the safe use of drugs, and this is usually achieved through the spreading of accurate, timely, and relevant information on clinical symptoms. Reporting potential harms to drug use by all physicians, pharmacists, nursing staff and patients is of the utmost priority. It is the responsibility of physicians and health staff in general to report these negative effects of the use of the drug. In this context, early detection of safety-related signals from clinical trials and post-marketing monitoring and supervision is essential to determine the risks associated with the products. The information gathered during the pre-marketing phase of drug development may not reveal some rare adverse drug reactions. The drug is used during clinical trials under controlled conditions, in addition to the limited and selectivity of the patients' number registered in the clinical trials. The usage of the drug may not be studied in special circumstances or among a specific population. Hence, monitoring after marketing the drug is extremely important [1,2]. Hereunder is analysis of the Pharmacovigilance Program in Aden.

The received spontaneous reports on the harmful effects of drugs during the monitoring phase after marketing the drug showed the detection of negative signs resulting from the use of the drug in certain population groups. The Supreme Commission for Medicines and Medical Supplies in our country is making a positive effort in developing the pharmacovigilance program and improving its level by monitoring various reports of the harmful effects of drugs and withdrawing certain types of drugs from the market, and this confirms the importance of focusing attention on the pharmacovigilance approach and increasing it. Concern about improving the current pharmacovigilance infrastructure and highlighting the need to ensure coordination between the systems driving the reporting process for side effects, the continuous monitoring of unwanted effects, and safety aspects of the drugs entering the market.

The strengths of the program are based on the good connection with the High Medicines Authority, which facilitated the procedures, about 27 medicines were withdrawn which described being ineffective and the reports reach 215 in 2019, which is a good number in the current war conditions, and many educational courses were held in hospitals and some training courses. This is a wonderful achievement in the current conditions of Yemen.

The main weaknesses of the program are the weak awareness among health professionals about pharmacovigilance, and difficulty generating signals due to the lack of a national computerized database of prescription drugs, poor coordination of the pharmaceutical industry's involvement on drug safety profile; absence of data generation on genetic

effects, community practices and drug interaction related with drug use; there are also a few reports of traditional and herbal medicines that have been in common use. Another major weakness of the program is the lack of reporting. The reasons for underreporting are uncertainty in the types of reporting responsibilities, and a lack of awareness about the existence, function, and purpose of the national vigilance centers. There is also no formal consumer and patient reporting system that limits reporting that takes place at the consumer level. Finally, the nursing staff was not involved in the adverse effects monitoring program.

Strategies to Upgrade the Current Pharmacovigilance Program

Several strategies can be taken to upgrade the current pharmacovigilance program in Yemen. Some of the suggested strategies are listed below:

An Awareness Program for Healthcare Professionals:

More awareness-raising programs should be conducted regularly for healthcare professionals with an emphasis on the importance and work of the National Pharmacovigilance Program.

Teaching pharmacovigilance:

Pharmacovigilance should be taught to the university-related medical, nursing, pharmacy, and other health care curricula to ensure well-prepared graduates in future practice. The pharmacovigilance units should be linked to the (Rational Use of Medicine) RUM center. The Uppsala Monitoring Center (UMC), the international cooperating center for monitoring the adverse effects of medicines, has proposed several essential components of a pharmacovigilance cycle for pharmacologists and other health care professionals.

Patient and Consumer Reporting:

Strategies must be taken to involve consumers in the Medicines Adverse Reporting Program. Currently, there is very little consumer participation in the pharmacovigilance program.

Educational Interventions: Studies have indicated that continuous visits to doctors, pharmacists, posters, and educational materials such as brochures and leaflets have a profound effect on improving reporting and saving patients from the harmful effects of medicines. The usefulness of pharmacovigilance actions in a country is based on the effective contribution of health experts, patients, and customers. The more data about ADRs has been gathered the better and more valuable results are obtained. Consequently, all should be briefed concerning the ADRs reporting system and encouraged to monitor ADRs even suspicious ones (4,14).

The Urgent Need of Pharmacovigilance of Biosimilars in Yemen

Improving the pharmacovigilance for biosimilars should be aware by the Physicians and researchers. Studies by researchers in India highlighted the complexity and heat lability of biosimilars. Biosimilars have a huge multipart structure, several industrial processes, and are made in an alive organism, which requires specific transport tools and limited heat controls to avoid degradation. Biosimilars need more comprehensive pharmacovigilance measures than generics and a similar

level of pharmacovigilance as their original products. The researchers also, suggested the continuation of the studies and pharmacovigilance reporting while a biosimilar is distributed in the market, as the composition of patient populations can alter and drug reliability can differ over time. Appropriate monitoring and hazard controlling are crucial for perfect pharmacovigilance activities which necessitate reporting all kinds of suspected responses, proposed drug-drug interactions or drug-food interactions, side-effects related to drug discontinuation, drug errors, or overdosing to regulatory authorities' ineffectiveness. A comprehensive pharmacovigilance program should include regular safety information reports and hazard control strategies. Many variables can affect the quality of the active ingredient of biosimilars while the transition from plant to clinic to the patient even if their manufacturing processes are safe and efficient. Patent problems can also influence the kinds of dispensing devices that can be used. Also, the volume and quality of the drug delivered can be affected by the delivery device due to close contact between the active ingredients and the delivery device. Therefore, the safety of the device delivery system for biosimilars is of dominant significance.

The temperature is among the most vital ecological parameter. Pharmacovigilance should take consideration of this point, which is commonly ignored until an issue for instance; the absence of effectiveness or immunogenicity is recognized. Yemen has some active substances for biosimilars registered by SBDMA as listed in Table 1. Here the first biosimilar was marketed for Erythrobiotin, the several-step manufacturing procedure for biosimilars is liable to differences that will influence the end product, counting immunogenicity, an important safety risk linked with biosimilars. The industrial procedure for biosimilars is recognized to influence the level of procedure-induced contamination and post-translational modifications of the product.

Biosimilars are given by injection-like generics, increasing safety and liability concerns about the delivery device. Some authors recommend monitoring manufacturing devices and assessing factors such as ease of use that could influence patient compliance. The researchers notice that infrequent adverse reactions frequently occur when several patients use a biosimilar. Consequently, biosimilars need post-market observation and possibly post-authorization studies to assess identifying formerly unidentified side effects of drug reactions and to better evaluate the hazards and benefits of a drug. Suitable pharmacovigilance needs expert and qualified workers (as with original biological products) due to the complicated safety information and the difficulty of detecting side effect reactions (2-4,10).

Biosimilars and Its Implication in Yemeni Pharmacy Practice

There are about eight biosimilars in the Yemeni markets as illustrated in Table (1). The are several regulatory challenges facing biosimilar medications, there must be a federal intervention to overcome the aforementioned barriers. However,

pharmacists in different practice settings could play an effective role in changes. The FDA and other monitoring agencies commonly request feedback by reporting side effect records to gather biosimilar safety information and enhance clinical practice. Pharmacists could send research or case studies including, interchangeability pharmacovigilance programs, or other practices to offer policymakers with actual-world data to assist in developing management files. Furthermore, in manufacturing and controlling affairs, pharmacists can be managers of enhanced biosimilar assessment. Pharmacists occupied by medicinal corporations will request to supervise the progress of clinical experiments to confirm that industries are manufacturing safe and active agents. Controlling affairs pharmacists might be engaged in biosimilar usage review, which includes clinical decisions when rereading the entirety of the suggestion offered by the industries. Pharmacists can play a guidance role in the aforementioned areas as they are qualified in biopharmaceutics, literature evaluation, and long-term safety data of biosimilar medications. After the marketing of biosimilars, the pharmacist will require to be alert of the applied, day-to-day management of biosimilar drugs.

As a part of an effective healthcare organization, pharmacists will be expected to participate in education, benefits confirmation, and medication admission. Pharmacists may require to reliably participate with patients to be sure that the patient follows the treatment schedules thus patients may continue to obtain aids or patient support. Moreover, some pharmacists may be enrolled in therapeutic medication monitoring, estimating patients for effectiveness or indication of immunogenicity or drug toxicity [22]. The Interchangeability between the biosimilars and reference biologic agents should be awarded by the pharmacists [23] and be alerted that each case has its parameters so Inappropriately substituting may be dangerous.

Table 1 : List of Active Substance for Biosimilars in Yemen**.**

No.	Generic name	Product	Dosage form	Agent	Company
1	Human albumin	ZENALB(TM)	Oral solution	AL-SALAMAH MEDICAL & TRADING CO. LTD	BIO PRODUCT LABORATORY (BPL) [UNITED KINGDOM]
2		ALBAPURE	Vial	ETHMAR TRADING LTD	CROMA PHARMA GMBH AUST(MA)P.F(RAFAA) [AUSTRIA]
3		HUMAN ALBUMIN	Iv injection	AL-MADINA MEDICAL CORPRATION	FARMACUBA [CUBA]
4		ALBUTEIN	Iv injection	ASHARQ TRADE & AGENCIES & OIL FIELDS SUP	GRIFOLS [UNITED STATES OF AMERICA]
5		HUMAN ALBUMIN	Iv injection	BILQUIS DRUGS STORES	HUMAN BIOPLAZMA MANUFACT. &TRADING LTD. [HUNGARY]
6		UMAN	vial	NASHWAN PHARMA CO LTD	KEDRION S.P.A [ITALY]
7		YDR ALBUM	Iv injection	AL-NAHDI MEDICALS CO .	L.F.B. [FRANCE]
8		HUMAN ALBUMIN	Iv injection	AL-FATH TRADING CO. Ltd .	OCTAPHARMA [AUSTRIA]
9		PLASBUMIN-20	Iv injection	SALLAM-PHARM TRADING	TALECRIS BIOTHERAPEUTICS [UNITED STATES OF AMERICA]
10		HUMAN ALBUMIN	Iv injection	ARRA'AFAH CORPORATION FOR DRUGS	BAXTER AG VIENNA AUSTRIA(RAFFAA) [AUSTRIA]
11		BUMINTE	Iv injection	ARRA'AFAH CORPORATION FOR DRUGS	BAXTER HEALTHCARE CORPORATION USA [UNITED STATES OF AMERICA]

Table 1: (continue) List of Active Substance for Biosimilars in Yemen

1	Anti-tetanus injection	TETANUS TOXOID	Ampoule	SISCO FOR MEDICINE&MEDICAL SUPP.CO.Ltd	SERUM INSTITUTE [INDIA]
2		TETANUS ONTI TOXIN	vial	NAGIB A	VINS BIOPRODUCTS LIMITED [INDIA]
1	ERYTHROPOIETIN injection	EPOFORM	vial	AL-MEITEMI CORPORATION FOR DRUGS	EIPICO [EGYPT]
2		EPOTIN	vial	ARD AL-GANNATEIN COMPANY	JULPHAR [UNITED ARAB EMIRATES]
3		EPOETINE	vial	AL-HARETH CORP. FOR DRUGS & MEDICINES	SEDICO [EGYPT]
1	Essential amino acid injection	ANOSOl	Iv Injection	AL-MEITEMI CORPORATION FOR DRUGS	SHIN POONG PHARMACEUTICAL CO. LTD [REPUBLIC OF KOREA]
2					
3		HIKMEN	Iv Injection	ABDUL HAFEED THABET SAIF HOUSES	BORYUNG PHARMA [REPUBLIC OF KOREA]
4		LEVOTASOL			
5		MARINASOL	Iv Injection	AL-MEITEMI CORPORATION FOR DRUGS	CHONG KUN DANG PHARMA [REPUBLIC OF KOREA]
6		RUCHIASOL			
7		CELEMIN 10 .PLUS	Iv Injection	ALABED MEDICAL SUPPLIES CO.LTD	CLARIS LIFESCIENCES [INDIA]
8		CELEMIN 5-S			
9		NEPHRISOL	Iv Injection	CRESCENT CANDLE FOR TRADING	DAIHAN PHARMA.CO.,LTD. [REPUBLIC OF KOREA]
10		SAERONAMIN			
11		AMINOLEBAN	Iv Injection	AL-FATH TRADING .CO. Ltd	OTSUKA (EGY) [EGYPT]
12		PAN-AMIN G			
13		PAN-AMIN SG			

Table 1: (continue) List of Active Substance for Biosimilars in Yemen

1	Heparin injection	HEPARIN SODIUM	Iv Injection	MOHAMMED MAHDI .AL-SHAER CORP	PANPHARMA [FRANCE]
2		HEPARIN-Na	Vial	ARRA'AFAH CORPORATION FOR DRUGS	SANDOZ GMBH [AUSTRIA]
3		HEPARIN-Ca	Ampoule		
4		HEPARIN	Vial	AL-MEITEMI CORPORATION FOR DRUGS	SHIN POONG PHARMACEUTICAL CO. LTD [REPUBLIC OF KOREA]
5					
6		RINHEPA	Vial	BAUAM BROTHERS TRADING EST .	United biotech(P) [INDIA]
7					
8		UNIPARIN-Ca	Vial	HILAL PHARMACY	WOCKHARD(MANUFCT.CP PHARMACEUTICAL UK) [UNITED KINGDOM]
9		UNIPARIN-Na			
10		HIKMA-HEPARIN	Vial	ARD AL-GANNATEIN COMPANY	AL-HIKMA [JORDAN]
11					
12					
13		HEPARODIC	Ampoule	MAGNICO FOR TRADING & AGENCIES .	CASPIAN TAMIN [ISLAMIC REPUBLIC OF IRAN]
14		ARAPIN	Vial	ALABED MEDICAL SUPPLIES CO.LTD	CLARIS LIFESCIENCES [INDIA]
15		HEPARIN	Vial	SISCO FOR MEDICINE&MEDICAL SUPP.CO. Ltd .	GLAND PHARMA [INDIA]
16		VAXCEL HEPARINE	Vial	DADIAH GENERAL TRADING	KOTRA PHARMA(M)SDN.BHD [MALAYSIA]
17		HEPARIN Na	Vial	ASHARQ TRADE & AGENCIES & OIL FIELDS SUP	LEO DENMARK [DENMARK]
18		HEPARIN-LEO			

Table 1: (continue) List of Active Substance for Biosimilars in Yemen

1	Serum & vaccine	DIPHTHERIA TET. VAC. ADU	Ampoule	SISCO FOR MEDICINE&MEDICAL SUPP.CO.Ltd	SERUM INSTITUTE [INDIA]
2		DIPHTHERIA TET. VAC. PED			
3		DIPHTHERIA TETANUS PERTUS			
4		MEASLES, MUMPS & RUBELLA			
5		MEASLES VACCINE, LIVE			
6		POLYVALINT ANTI-SNAKE VEN			
7		RABIVAX			
8		RUBELLA VACCINE			
9		SCORPION VENOM ANTISERUM	Vial	NAGIB A	VINS BIOPRODUCTS LIMITED [INDIA]
10		SNAKE VENOM ANTISERUM			
11		VINRAB			
12					
13		SNAKE VENOM .ANTISERUM	Vial	ALFA PHARMA. COR	BHARAT SERUM&VACCINES Ltd [INDIA]

Table 1: (continue) List of Active Substance for Biosimilars in Yemen.

1	Immunoglobulin Human	OCTAGAM	Iv injection	AL-FATH TRADING CO. Ltd	OCTAPHARMA [AUSTRIA]
2		EQUIRAB			
3		RHOCLONE FREEZE DRIED	Iv injection	ALFA PHARMA. COR	BHARAT SERUM&VACCINES Ltd [INDIA]
1	Insulin	INSUGEN - 30/70(biphasic)	Vial	AL-KHALIL FOR DRUG	BIOCON LIMITED [INDIA]
		INSUGEN-N ISOPHAN			
2		INSUGEN-R SOLUBLE			
3		JUSLINE	Vial	ARD AL-GANNATEIN COMPANY	JULPHAR [UNITED ARAB EMIRATES]
4		JUSLINE N			
5		JUSLINE R			
6		ACTRAPID HM	Vial	ARRA'AFAH CORPORATION FOR DRUGS	NOVO NORDISK [DENMARK]
7		ACTRAPID NOVOLET			
8		INSULATARD HM			
9		INSULATARD NOVOLET			
10		MIXTARD			
11		MIXTARD 30 HM			
12		APIDRA SOLOSTAR	ampoule	NATCOPHARMA	SANOFI AVENTIS GERMANY(NATCO) [GERMANY]
13		LANTUS	Vial		
14		INSULIN H BIO NPH	Vial	AL-HARETH CORP. FOR DRUGS & MEDICINES	SANOFI AVENTIS GERMANY(NATCO) [GERMANY]
15		INSULIN H MIX			
16		INSULIN H BIO R			
17		INSULET NPH	Vial	BAWAM FOR MEDICINES	SOTHEMA [MOROCCO] VACSERA [EGYPT]
18		INSULET RAPID			
19		HUMAN .INSULIN MIX	Vial	AL-FATH TRADING CO. Ltd BAWAM FOR MEDICINES	VACSERA [EGYPT]
20		HUMAN INSULIN R			
21		HUMAN INSULIN N			

Conclusion

The availability of biosimilars as lower-cost biologics must wisely consider issues of safety, efficacy, and traceability. Strict pharmacovigilance procedures are needed to evaluate the potential variations in safety indications between biosimilars and their reference products and recognize the adverse drug reactions with biologics and biosimilar products. Pharmacovigilance of biologics should contain procedures that are straightforwardly used by prescribing practitioners to guarantee that data are reliable and new safety signals are appropriately reported and allocated to the precise and accurate product.

Recommendations

It is clear that pharmacists could play a crucial role in overseeing the introduction of biosimilars into the healthcare systems. Therefore, it needed to provide the depiction data on the availability of biosimilars in Yemen. Further study is needed to understand the interchangeability of biological and chemical alternatives of the biosimilars in Yemen.

Some specific recommendations should be followed by the interested parties to enhance approval and safe use of biosimilars:

1. Evaluation and analysis of the biosimilars by the regulatory authorities should be improved. Staff should have suitable skills and expertise, also knowledge sharing between the health authorities is a must.
2. Working groups should be established in different parts of Yemen under the supervision of the Minister of Public Health and Population to share their regulatory experience and plans related to biosimilars.
3. Each governorate in Yemen should establish its working group, including experts with interest in biosimilars, to support regulatory authorities in their efforts to introduce biosimilars into their particular governorates.
4. The pharmacovigilance efforts should be encouraged by training health staff and increasing awareness about reporting the adverse effects of drugs including biosimilars and analyzing the related data.
5. Products that are accepted as ‘intended copy’ biological drugs should be assessed according to regulations specific to biosimilars. It should not be supposed that a previously accepted biopharmaceutical is a biosimilar, irrespective of existing clinical experience. Reconsideration is important and the pharmaceutical company should carry the required studies on time.

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References

1. European Medicines Agency. Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2014.
2. Nick C. The US Biosimilars Act: Challenges Facing Regulatory Approval. Pharm Med 26 (3): 145–52. doi:10.1007/bf03262388. S2CID 14604362.
3. Lamanna WC, Holzmann J, Cohen HP, Guo X, Schweigler M, Stangler T, *et al*. "Maintaining consistent quality and clinical performance of biopharmaceuticals". Expert Opinion on Biological Therapy. 2018; 18 (4): 369–79. doi:10.1080/14712598.2018.1421169.
4. World Health Organization. Guidelines on evaluation of similar Biotherapeutic Products (SBPs). 2009.
5. World Health Organization. Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, Technical Report Series No. 977, 2013.
6. World Health Organization. WHO Questions and Answers: Similar Biotherapeutic Products, 2018.
7. World Health Organization. Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 1004. 2017
8. Awad M, Singh P, Hilas O. Zarxio (Filgrastim-Sndz): The first biosimilar approved by the FDA. Pharmacy and Therapeutics 2017; 42(1): 19.
9. EMA. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. https://www.ema.europa.eu/en [cited in 5 Sep. 2020].
10. Shaw BE, Confer DL, Hwang WY, Pamphilon DH, Pulsipher MA. Concerns about the use of biosimilar granulocyte colony-stimulating factors for the mobilization of stem cells in normal donors: position of the World Marrow Donor Association. J Ferrata-Storti Foundation 2011; 97(7):942-7.
11. Kabir ER, Moreino SS, Siam M. KS. The breakthrough of biosimilars: a twist in the narrative of biological therapy. Biomolecules 2019; 9(9): 410.
12. Mellstedt H. Niederwieser D. Ludwig H. The challenge of biosimilars. Ann Oncol 2008; 19: 411-9.
13. World Health Organization. Pharmacovigilance. WHO, Geneva, Switzerland. https://www.cmedresearch.com/services/medical/drugsafety/?gclid=cjwkcajwwab7brbaeiwaapqptkrswzdq1uvgbcxwbkp71vshnzap62d1-xhrr-k5fwvq2vfe_hvclroco1yqavd_BwE [cited in 10 Sep. 2020].
14. Giezen TJ, Straus SM, Mantel-Teeuwisse AK. Pharmacovigilance of biosimilars from a regulatory point of view: Is there a need for a specific approach? International Journal of Risk & Safety in Medicine 2009; 21(1-2): 53-8.
15. Ebbers HC, Crow SA, Vulto AG, Schellekens H. Interchangeability, immunogenicity and biosimilars". Nature biotechnology 2012; 30(12):1186-90.

16. Republic of Yemen, Ministry of Public Health and the Population, WHO. Pharmaceutical Country Profile, 2011.
17. Camacho LH. Current status of biosimilars in oncology. Drugs 2017; 77(9): 985-97.
18. Casadevall N, Edwards IR, Felix T, Graze PR, Litten JB, Strober BE, *et al*. Pharmacovigilance and biosimilars: considerations, needs and challenges. Expert Opinion on Biological Therapy 2013; 13(7): 1039-47.
19. Kang H-N, Thorpe R, Knezevic I. The regulatory landscape of biosimilars: WHO efforts and progress made from 2009 to 2019. Biologicals 2020; 65: 1–9.
20. Alshakka M, Abdorabbo A, Basaleem H, Jha N, Alshammari T, Shankar R. Knowledge, attitude beliefs and practices of community pharmacy dispensers in Aden, Yemen towards adverse drug reaction reporting World J Pharmaceutical Sciences 2015; 3(10): 2111-8.
21. Alshakka M, Bassaleem H, Alsakkaf K, Mokhtar M, Alshagga M, AL-Dubai S, *et al*. Knowledge and perception towards pharmacovigilance among Healthcare professionals in Tertiary Care Teaching Hospital in Aden, Yemen. J Pharm Prac Community Med 2016;2(1):21-8.
22. Hobbs AL, Crawford JP. Biosimilars and implications for pharmacy practice: Ready or not, here they come! Pharmacy Practice 2019;17(3):1659. https://doi.org/10.18549/PharmPract.2019.3.1659
23. US Food & Drug Administration. Purple Book: Lists of Licensed Biological Products. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or (cited in Oct 5, 2020).