Biomedical Sciences
2019; 5(4): 60-66
http://www.sciencepublishinggroup.com/j/bs
doi: 10.11648/j.bs.20190504.14
ISSN: 2575-3924 (Print); ISSN: 2575-3932 (Online)

Review Article

Biosimilars: Past, Present, and Future

Abdul Alim[1], Ahasanul Hasan[2], Abu Syed Md. Anisuzzaman[3, *]

[1]Department of Pharmacy, University of Rajshahi, Rajshahi, Bangladesh

[2]Department of Clinical Pharmacy & Pharmacology, University of Dhaka, Dhaka, Bangladesh

[3]Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, USA

Email address:
alimreza_pharma@yahoo.com (A. Alim), ahhasan.cpp@du.ac.bd (A. Hasan),
abu.syed.md.anisuzzaman@emory.edu (A. S. Md. Anisuzzaman)

[*]Corresponding author

To cite this article:
Abdul Alim, Ahasanul Hasan, Abu Syed Md. Anisuzzaman. Biosimilars: Past, Present, and Future. *Biomedical Sciences*. Vol. 5, No. 4, 2019, pp. 60-66. doi: 10.11648/j.bs.20190504.14

Received: October 18, 2019; **Accepted**: November 7, 2019; **Published**: November 21, 2019

Abstract: The expiry of patent of biologic medicines emerged the development and manufacturing of biosimilar products worldwide. A number of biologic medicines have successfully been developed and approved over the last one and half decades, enlightening the lives of patients globally. According to the European Medicines Agency (EMA), biosimilar product can be defined as a biological medicine that is highly similar to another biological medicine that has already been authorized for use. Biological medicines contain active substances from a biological source, for example, living cells or organisms (human, animals and microorganisms: bacteria or yeast) and are often manufactured by cutting-edge technology. Most of the biological medicines in current clinical use comprise of active substances made of proteins. Biopharmaceuticals contain a wide-range of products such as vaccines, immunoglobulins, monoclonal antibodies, cell and gene therapy products. The EMA led the way (well ahead of the Food and Drug Administration in the US) in evolving the biosimilar idea, and the type of science-based regulatory framework required to ensure high-quality, safe, and effective biosimilar medicines; the provisions for approval of biosimilars have been in place in Europe since the year 2005. Under these provisions, Omnitrope® (Somatropin-Sandoz-Novartis) was approved by the EMA in the year 2006 as the world's first biosimilar medicine; the US Food and Drug Administration (US-FDA) approved Zarxio™ (Filgrastim-Sandoz) for all indications included in the reference product's label in March 2015. Zarxio™ (Sandoz-Novartis) is the first biosimilar product approved by US-FDA.

Keywords: Biosimilars, Biologic Medicines, Biopharmaceuticals, European Medicines Agency (EMA), The US Food and Drug Administration (US-FDA), World Health Organization (WHO), Immunogenicity, Pharmacovigilance

1. Introduction

Most of the countries around the globe encounter the common problems of elderly population and the associated increase in the widespread occurrence of chronic diseases. The success of biotherapeutic products has led to increased interest in the development of biosimilars. The patents of several best-selling biotherapeutic products have already been expired and will reach their expiry date very soon. For example, the patent on the breast cancer drug Herceptin, a monoclonal antibody (mAb) with international non-proprietary name-Trastuzumab, already expired in July 2014 in the European Union (EU) and in June 2019 in the United States of America [1].

A biosimilar is a biological medicine, a medicine whose active substance is made by a living organism, highly similar to another already approved ('reference medicine') biological medicine. Biosimilars are approved as per the same standards of pharmaceutical quality, safety and efficacy that are applicable for all biological medicines. Biological medicines offer effective treatment options for patients who suffer from chronic and often disabling conditions such as diabetes, autoimmune disease and cancers. They contain active

substances from a biological source and are generally produced by cutting-edge technology. In current clinical use, most of the biological medicines contain active substances made of proteins. The proteins can vary in size and structural complexity, from simple proteins like insulin or growth hormone to more complex ones, for instance, coagulation factors or monoclonal antibodies [2, 10, 15]. As per Therapeutic Goods administration (TGA) Australia, a similar biological medicinal product (SBMP) is a form of an already registered biological medicine that has a significant similarity in properties (physicochemical, biological and immunological), efficacy and safety, based on comprehensive comparability studies [19].

A manufacturer developing a proposed biosimilar ensures that its product is highly similar to the reference product by broadly characterizing the structure and function of both the reference product and the proposed biosimilar as well. State-of-the-art technology is used to compare characteristics of the products: purity, chemical identity, and bioactivity. Comparative study results are necessary for manufacturer to demonstrate that the biosimilar is highly similar to the reference product. Minor variation (stabilizer or buffer) between the reference product and the proposed biosimilar product in clinically inactive components are acceptable. Any minor differences between the proposed biosimilar product and the reference product are carefully evaluated by FDA to ensure the biosimilar meets FDA's high approval standards [3]. Biosimilars are different from generic drugs due to the larger molecule and its complex structure of the active ingredients. That sort of molecules is nearly impossible to replicate in every detail, even by the original manufacturer, minute variations in production yield significance differences [12].

A significant number of biologic medicines have been developed and approved over the past decade for the treatment of patients with certain diseases globally. The price of biologic medicines is not cheap, and the patent of some biological medicines had already been expired. Since biologics lose their patent-protection, many biosimilars are becoming available across Europe and America and many other parts of the world, and manufacturers are seeking to bring additional biosimilar products to market. The initiatives are accelerating the way to generate competition for biologic therapies and thereby lower costs and increase patient access [8].

2. Discussion

2.1. Development, Review and Approval of Biosimilars

Biosimilars are very expensive and onerous to manufacture than the generic forms of small-molecule drugs. Usually 5–10 years and an investment of US$100 million–250 million are required to bring a biosimilar to the market for patients, compared with about 2 years and $1 million–10 million to develop a conventional generic drug [8].

(i) Reverse engineering: Various analysis methods, such as mass spectroscopy, are used to determine the amino-acid sequence, protein structure and any chemical modifications of original biologic. Then the profiles obtained are compared with those of future biosimilars [8].
(ii) Cell-culture conditions: Varieties of cell lines can produce variants of a particular protein, even when following the same genetic instructions. Therefore, to ensure that the product closely resembles the original biologic biosimilar, developers must identify an appropriate cellular factory, and optimize those cells' growth conditions very carefully [8].
(iii) Testing the function: Different assay methods are used to test prospective biosimilar binding to its biosimilar target, and to ensure the biosimilar drug replicates the effect and specificity of the original biologic [8].
(iv) Finding the formulation: Biosimilar products developers must identify the manufacturing processes that produce a stable and reliable product. If a biologic medicine is not appropriately manufactured or blended, it can misfold, degrade or aggregate [8].
(v) Clinical confirmation: Clinical trial of a biosimilar in people is faster than evaluating a biologic medicine. Usually, only a phase-I trial to exhibit that the drug is safe and a phase III trial to exhibit that it has an efficacy similar to that of the original are required [8].
(vi) Regulatory review: Depend on the clinical data available, a regulatory authority decides whether a biosimilar is sufficiently similar to the original biologic [8].

The manufacturer of a proposed biosimilar product generates a collection of data relating the proposed product to the FDA-approved reference product in order to explain biosimilarity. The comparative data are generated and evaluated in a step by step that begins with a foundation of detailed analytical characterization and comparison of the products, moving on to animal studies if required and then to comparative clinical studies. Therefore, a manufacturer that shows its proposed biosimilar product is highly similar to and has no clinically meaningful differences from the FDA-approved reference product [18].

Scientific committees of EMA evaluate the majority of marketing authorization applications for biosimilar medicines before they can be approved and marketed in the EU. EMA applies the same rules during evaluation of biosimilars according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines approved in the EU. Developers of biosimilars are required to demonstrate through comprehensive comparability studies with the 'reference' biological medicine that: (a) their biological medicine is highly similar to the reference medicine, despite natural variability inherent to all biological medicines; (b) no clinically meaningful differences can be between the biosimilar and the reference medicine in terms of safety, quality and efficacy. This allows eliminate the unnecessary redundancy of clinical trials already carried out with the reference medicine. Biosimilar manufacturers and marketers should improve patient access to safe and effective biological medicines with proven quality.

Table 1. *Comparison of data requirements for approval of a biosimilar and the reference medicine.*

Reference medicine	Biosimilar medicine
Risk management plan	Risk management plan
Clinical studies: Safety and efficacy, PK/PD, Immunogenicity.	Comparative clinical studies: Safety and efficacy, PK/PD, Immunogenicity.
Non-clinical studies	Comparative Non-clinical studies, comparative quality studies
Pharmaceuticals quality studies	Pharmaceuticals quality studies

Biosimilars can only be authorized after the expiry of data exclusivity on the 'reference' biological medicine. Generally, this means that the biological reference medicine must have been authorized for at least eight years prior to another company can apply for approval of a similar biological medicine [6].

In order to market a medicinal drug as biosimilar in Japan, the guidelines of the International Conference on Harmonization (ICH) should be followed: guideline Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process and guideline Q6B: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. For the biosimilar development and approval in Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan collaborates with the pharmaceutical industry [11].

Moreover, it is hard to establish therapeutic equivalence of biosimilars with reference products without clinical trials; consequently, their market approval is more complicated. Actually, registration of biosimilars involves more stringent evaluation than is required for conventional generics, and, applications for marketing authorization must be accompanied by thorough comparability studies to demonstrate the similarity of the proposed biosimilar to the reference product regarding quality, safety and efficacy [13].

2.2. Approved Biosimilars

Omnitrope (Somatropin), manufactured by Sandoz GmbH (Novartis), was the first biosimilar product approved by European Medicines Agency (EMA) in April 2006 [3]. The US Food and Drug Administration (FDA) approved Zarxio™ (Filgrastim-Sandoz) for all indications included in the reference product's label in March 2015. Zarxio is the first biosimilar product approved by US-FDA [5].

Table 2. *European Medicines Agency Approved Biosimilars (April 2017) [4].*

Name of product (Active substance), Company	Date of Approval
Omnitrope (Somatropin), Sandoz, Novartis	April 2006
Abseamed (Epoetin alfa), Medice Arzneimittel Pütter GmbH & Co. KG	August 2007
Binocrit (Epoetin alfa), Sandoz GmbH	August 2007
Epoetin Alfa Hexal (Epoetin alfa), Hexal AG	August 2007
Retacrit (Epoetin zeta), Hospira UK Limited	December 2007
Silapo (Epoetin zeta), Stada Arzneimittel AG	December 2007
Ratiograstim (Filgrastim), Ratiopharm GmbH	September 2008
Tevagrastim (Filgrastim), Teva GmbH	September 2008
Zarzio (Filgrastim), Sandoz GmbH	February 2009
Filgrastim Hexal (Filgrastim), Hexal AG	February 2009
Nivestim (Filgrastim), Hospira UK Ltd	June 2010
Remsima (Infliximab), Celltrion Healthcare Hungary Kft.	September 2013
Inflectra (Infliximab), Hospira UK Limited	September 2013
Ovaleap (Follitropin alfa), Teva Pharma B.V.	September 2013
Grastofil (Filgrastim), Apotex Europe BV	October 2013
Bemfola (Follitropin alfa), Gedeon Richter Plc.	March 2014
Abasaglar (previously Abasria) (Insulin glargine), Eli Lilly Regional Operations GmbH	September 2014
Accofil (Filgrastim), Accord Healthcare Ltd	September 2014
Benepali (Etanercept), Samsung Bioepis UK Limited	January 2016
Flixabi (Infliximab), Samsung Bioepis UK Limited	May 2016
Inhixa (Enoxaparin sodium), Techdow Europe AB	September 2016
Thorinane (Enoxaparin sodium), Pharmathen S.A.	September 2016
Lusduna (Insulin glargine), Merck Sharp & Dohme Limited	January 2017
Terrosa (Teriparatide), Gedeon Richter Plc.	January 2017
Movymia (Teriparatide), STADA Arzneimittel AG	January 2017
Truxima (Rituximab), Celltrion Healthcare Hungary Kft.	February 2017
Solymbic (Adalimumab), Amgen Europe B.V.	March 2017
Amgevita (Adalimumab), Amgen Europe B.V.	March 2017

Table 3. *Biosimilars under review by EMA (April 2017) [4].*

Common Name	Therapeutic Area	Originator product	Originator company
Adalimumab	Immunosuppressant	Humira	AbbVie Ltd
Bevacizumab	Antineoplastic medicines	Avastin	Roche
Etanercept	Immunosuppressant	Enbrel	Amgen
Insulin glargine	Diabetes	Lantus	Sanofi-Aventis
Insulin lispro	Medicines used in diabetes	Humalog	Eli Lilly
Pegfilgrastim	Immunostimulants	Neulasta	Amgen

Common Name	Therapeutic Area	Originator product	Originator company
Rituximab	Antineoplastic medicines	MabThera	Roche
Trastuzumab	Antineoplastic medicines	Herceptin	Roche

Table 4. *US-FDA Approved Biosimilar Products [5].*

Name of Drug	Date of Approval	Name of Drug	Date of Approval
Hadlima (Adalimumab-bwwd)	July 2019	Fulphila (Pegfilgrastim-jmdb)	June 2018
Ruxience (Rituximab-pvvr)	July 2019	Retacrit (Epoetin alfa-epbx)	May 2018
Zirabev (Bevacizumab-bvzr)	June 2019	Ixifi (Infliximab-qbtx)	December 2017
Kanjinti (Trastuzumab-anns)	June 2019	Ogivri (Trastuzumab-dkst)	December 2017
Eticovo (Etanercept-ykro)	April 2019	Mvasi (Bevacizumab-awwb)	September 2017
Trazimera (Trastuzumab-qyyp)	March 2019	Cyltezo (Adalimumab-adbm)	August 2017
Ontruzant (Trastuzumab-dttb)	January 2019	Renflexis (Infliximab-abda)	May 2017
Herzuma (Trastuzumab-pkrb)	December 2018	Amjevita (Adalimumab –atto)	September 2016
Truxima (Rituximab-abbs)	November 2018	Erelzi (Etanercept-szzs)	August 2016
Udenyca (Pegfilgrastim-cbqv)	November 2018	Inflectra (Infliximab-dyyb)	April 2016
Hyrimoz (Adalimumab-adaz)	October 2018	Zarxio (Filgrastim-sndz)	March 2015 (FDA approved first biosimilar)
Nivestym (Filgrastim-aafi)	July 2018	----------	----------

Table 5. *Comparison of generic, biosimilar, and innovator products (Biologic) [7].*

Process	Innovator product (Biologic)	Biosimilar	Generic
Manufacturing	Manufactured by biological process in host cell lines More sensitive to production process changes. Reproducibility: difficult to establish	Manufactured by biological process in host cell lines More sensitive to production process changes. Reproducibility: difficult to establish	Manufactured by using chemical synthesis Less sensitive to production process changes Reproducibility: easy to establish
Clinical development	Widespread clinical studies, including Phase I–III, is required Pharmacovigilance and periodic safety data is required	Widespread clinical studies, including Phase I–III, is required Pharmacovigilance and periodic safety data is required	Short timeline is required for approval
Regulation	"Comparability" study is required	"Similarity" study is required	Bioequivalence study is required

2.3. Manufacturing of Biosimilars

The manufacturing of biologic medicines relies on recombinant DNA technology. Recombinant technology offers two distinct benefits. Firstly, entirely human proteins can be produced in non-human species. Secondly, the process is very adjustable. Certainly, this ability to scale up manufacture depends on the innate reliability of these processes in nature, which have advanced to produce proteins accurately and repeatedly using template-based approaches [14]. Manufacturing a biologic medicine comprises genetically modifying a cell. The genetically modified cell becomes the basis for a cell line used for the production of the necessary proteins for the biologic medicine. Then the protein is separated from the cells and purified. Biosimilars are produced from small changes in the manufacturing process which creates a molecule that is not identical but closely similar to the reference product. The slight difference in biosimilar molecule changes in the manufacturing process of a biosimilar can affect the efficacy and safety of a biosimilar compared to the reference biologic medicine. The manufacturing process for proteins has become more standardized and the required technology has become increasingly accessible over the last one and half decades, results in reduction of biosimilars production costs [20]. The manufacturing process for biologics can be divided into seven stages: (i). Host-cell development and cell culture, (ii). Master cell bank establishment & characterization, (iii). Protein production, (iv). Protein purification, (v). Analysis, (vi). Formulation and, (vii). Storage and handling [14].

2.4. Quality, Safety and Efficacy of Biosimilar Products

The quality, safety, and efficacy of a biosimilar product must be approved by the relevant regulatory body (for example, EMA, US-FDA) before marketing approval can be obtained [7]. Biosimilars have a product life-cycle like other biological medicines, commences with research and development and continues through manufacturing to regulatory evaluation of quality, safety and efficacy for both licensing and post-licensing oversight. However, the life-cycle of a biosimilar is unique in the logic that its regulatory approval depends on the safety and efficacy data and knowledge acquired during the development and licensing of an originator, or reference product [1].

The safety and efficacy of a biosimilar is established by explaining its similarity to a reference product. The extrapolation of data is used for the licensure of biosimilars, it is an established scientific and regulatory code that has been exercised for many years, for example, in considering changes to manufacturing processes of the originator biologicals. Regulators have learned the acceptable variation between different versions of a product from their experience with post-approval manufacturing changes. Prescribers, for instance physicians and clinicians, tend to verify the safety and efficacy of medicines by clinical trial data. Usually, analytical assessments are more sensitive for detecting

differences between, or changes in, products. Therefore, a biosimilar with chemical, physical and biological properties that are highly analogous to those of the reference product would be expected to exhibit the same pharmacological characteristics as the reference product and a similar safety and efficacy profile for every clinical indication [1]. Methods for quality assessment of biosimilars: Ion exchange; High performance liquid chromatography; Antibody-dependent cell-mediated cytotoxicity; Complement-dependent cytotoxicity; Capillary electrophoresis; Liquid chromatography–mass spectroscopy; Mass spectrometry; Electrospray ionization; Matrix-assisted laser desorption/ionization time of flight MS; Analytical ultracentrifugation; Cation exchange; Isoelectric focusing; Size exclusion; Reverse phase HPLC; Enzyme-linked immunosorbent assay [7].

2.5. Immunogenicity

Immunogenicity is the capability of a specific substance to simulate the production of antibodies in the human body. Possible immunogenicity is a key issue for biosimilars and may have serious clinical aftermath. Indeed, all biopharmaceuticals, in contrast to conventional drugs, demonstrate a greater capacity to stimulate antibodies and to make immune reactions [13]. Biosimilars may start an immune response, resulting in either loss of efficacy, development of neutralizing antibodies to the native endogenous hormone, or, less likely, increased potency. This risk of immunogenicity is of paramount concern, and related to route, duration and frequency of administration as well as the patient's underlying disease process and concurrent medication [17].

Immunogenicity is the most critical safety concern relating to biopharmaceuticals. All biopharmaceuticals are biologically active molecules derived from living cells and have the potential to induce an immune response. Although chemical or structural analysis of the biopharmaceutical cannot predict immunogenic potential, several factors are known to affect a product's immunogenic potential. Immunogenicity can be increased due to the presence of impurities in the final product, structural modifications as a result of the manufacturing process and/or storage conditions. Quality control procedures integrated into the manufacturing process can ensure the manufacture of safe products of consistent quality. The route of administration of the biopharmaceuticals may also affect immunogenicity reaction, for example, intravenous administration being less immunogenic than intramuscular or subcutaneous administration. Patient factors are also important in immunogenicity, such as genetic background and what type of disease is being treated and the patient's immune system [15].

The risks of immunogenicity can be mitigated by stringent testing of the biopharmaceuticals during its development. The tests are carried out *in vitro* and in vivo as well. All of these tests can provide an idea of the antigenic potential of a biopharmaceutical, but cannot predict its immunogenic effects in an individual patient. For a meaningful comparison of results, all assays used require to be standardised according to international guidelines and recommendations. The only prominent way of establishing the safety of a biopharmaceutical is the use of clinical trials. Long-term observation of the effects in patients must be prioritized in order to properly assess the immunogenic effects of any biopharmaceutical launched to the market [15].

2.6. Risk Management

Risk management can be defined as the comprehensive and proactive application of scientifically based methodologies to identify, assess, communicate and mitigate risk throughout a drug's life cycle so as to establish and maintain a favourable benefit–risk profile in patients. The management of a single risk can be considered as having four steps: (i) risk detection, (ii) risk assessment, (iii) risk minimization and (iv) risk communication. However, any biological or biosimilar medicinal product will have multiple risks associated with it and individual risks will vary with respect to severity, and individual patient and public health impact. Therefore, the concept of risk management should consider the combination of information on numerous risks to make sure that the benefits outweigh the risks by the greatest possible margin both for the individual patient and at the population level as well. The risk management system has two basic components: pharmacovigilance and risk minimization [11].

2.7. Costs of Biosimilars

Biosimilars have attracted the interest of health care providers mainly due to the potentially significant cost-savings biologic products may offer. In the year 2004, sales of over $20 billion (more than one third of total global biotechnology sales) were derived from the group of biopharmaceuticals represented by insulin, epoetin, GH, colony-stimulating factors and interferon a and b alone. The initial trend of Biosimilars could generate cost-savings equivalent to over $2 billion for European health care providers, as per suggestion of experts. However, more obstacles must be overcome in bringing a biologic product to market than a generic product; there is no accelerated approval process in place for Biosimilars. Currently, a full development program is needed, but follow-on biologics (FoB) manufacturers are struggling to change that situation. The biosimilar manufacturer must consider the costs of an extensive developmental program. It could be assumed that if the technology and knowledge are available to the manufacturer of the originator product, it could be used to help the FoB manufacturer to produce an identical product. In fact, newer innovative production techniques may supply a possible area of cost saving for the FoB manufacturer. Nevertheless, the master cell lines and details of manufacturing processes involved in producing an originator product are extremely guarded corporate secrets and are not part of the patent, but are the property of the originator company [16].

2.8. Pharmacovigilance of Biosimilar Products

For the marketing authorization procedure, the applicant should present a risk management plan/pharmacovigilance plan as per current EU legislation and pharmacovigilance guidelines. Risk mitigation activities in place for the reference medicinal product may have to be implemented into the Risk Management Plan of the biosimilar. For further safety considerations, applicants should provide at the time of MAA (Marketing Authorization Application) a comprehensive concept how to further study safety in a post-authorization setting: (i) safety in indications licensed for the reference mAb (mono-clonal antibody) claimed based on extrapolation of efficacy and safety data, including long term safety data unless otherwise justified; (ii) occurrence of rare and particularly severe adverse effects described and predicted, based on the pharmacology, for the reference mAb; (iii) the pharmacovigilance plan should be commensurate to identified and potential risks and should be informed by the safety specification for the reference mAb in addition to relevant knowledge regarding similar biological products as appropriate; (iv) detection of new safety signals, as for any other biological medicinal product; (v) activities to gain additional immunogenicity data, if needed [9].

Based on the handling of biosimilars and reference medicinal products in clinical practice at national level, 'switching' and 'interchanging' of medicines containing mAb might occur. Therefore, applicants are recommended to follow further development in the field and consider these characteristics as part of the risk management plan [9]. Elements of the pharmacovigilance system [11]: (a). Qualified Person responsible for pharmacovigilance (QPPV), (b). Organization, (c). Documented procedures, (d). Databases, (e). Contractual arrangements with other persons or organizations involved in the fulfilment of pharmacovigilance obligations, (f). Training, (g). Documentation, (h). Quality management system and (i). Supporting documentation.

2.9. Future of Biosimilar Products

Biosimilars provide alternative treatment options competing with the originator's biotherapeutic products, by this means reducing the price of these biotherapeutics and increasing their availability. However, improving access to biosimilars and ensuring their appropriate uses requires a high degree of collaboration between all stakeholders (for example, physicians, nurses, pharmacists, patients, manufacturer). The prime responsibilities of regulatory authorities are to provide regulatory oversight of biosimilars throughout their product life-cycle and to make sure that only high-quality, safe and efficacious biosimilars are available in the market. Regulatory authorities should monitor the proper use of biosimilars in public health systems in collaboration with other stakeholders. WHO has established global standards to ensure the quality, safety and efficacy of biotherapeutics, including biosimilars, at all phases of their life-cycle. These standards could serve as a foundation for mutual recognition of regulatory oversight and for regulatory junction at the global level [1].

3. Conclusion

Biosimilars are the biological medicines that are highly similar to the reference biological product. Since biosimilars are very sensitive to changes in the manufacturing process and the environment, stringent control needs to be ensured during the development and manufacturing stages. The patent of many biologic medicines has already been expired and will expire in the years to come, the development and manufacturing of several biosimilars would be one of the most effective ways in treating varieties of debilitating and fatal diseases. As biosimilars induce immunogenicity reaction, regulatory body must ensure the pharmacovigilance of biosimilars properly to forestall untoward consequences. Furthermore, manufacturers, stakeholders and regulatory authority should ensure the patients easy access to biosimilars in terms of costs.

Conflict of Interest

The authors declare no conflicts of interest in this review work.

References

[1] Bulletin of the World Health Organization (WHO). Regulatory evaluation of biosimilars throughout their product life-cycle. https://www.who.int/bulletin/volumes/96/4/17-206284/en/ Assessed on: 08 August 2019.

[2] EMA Biosimilar medicines: Overview. https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview Assessed on 09 August 2019.

[3] US-FDA: Biosimilar and Interchangeable Products. https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products#biosimilar. Assessed on 09 August 2019.

[4] Quintiles IMS: The impact of biosimilar competition in Europe 2017 (last update 5 May 2017). http://ec.europa.eu/docsroom/documents/23102/attachments/1/translations/en/renditions/pdf Accessed on 05 August 2019.

[5] US-FDA Biosimilar Product Information. http://www.fda.gov/grugs/biosimilars/biosimilar-product-information. Accessed 05 August 2019.

[6] EMA Biosimilar medicines: Development and Approval of Biosimilar. https://www.ema.europa.eu/en/humanregulatory/overview/biosimilar-medicines-overview Assessed on 10 August 2019.

[7] Biosimilar: An overview. Bhupinder Singh Sekhon, Vikrant Saluja, Drovepress: Biosimilars 2011:1 1–11. https://www.dovepress.com/biosimilars-an-overview-peer-reviewed-article-BS

[8] Nature: Bring on the biosimilars. (Outline May 2019), https://www.nature.com/articles/d41586-019-01401-5. Assessed on 08 August 2019.

[9] EMA Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. https://www.ema.europa.eu/en/documents/scientific guideline/guideline-similar-biological-medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf, Assessed on 15 August 2019.

[10] Comparing Originator Biologics and Biosimilars: A Review of the Relevant Issues. Corrado Blandizzi, et al, Journal of Clinical Therapeutics (2017), http/dx.doi.org/10.1016/j.clinthera.2017.03.014.

[11] Biosimilars: pharmacovigilance and risk management, Leyre Zuniga Ph.D. and Begona Calvo Ph.D. Pharmacoepidemiology and Drug Safety, 2010; 19: 661–669. Published online 7 May 2010 in Wiley Inter Science (www.interscience.wiley.com) DOI: 10.1002/pds.1948.

[12] Drug development: 'Biosimilar' drugs poised to penetrate market, News in focus, Nature| Vol 468|4 November 2010.

[13] An introduction to safety issues in Biosimilars/follow-on Biopharmaceuticals, Filiz Hincal, J Med CBR Def | Volume 7, 2009.

[14] An introduction to biologics and biosimilars. Part-II: Subsequent entry biologics: Biosame or Biodifferent? Peer-Reviewed, *Leigh Revers, MA, DPhil; Eva Furczon, HBSc, MBiotech,* C P J / R P C • July / August 2 0 1 0 • Vol 1 4 3, No. 4, P184-191.

[15] Biosimilars: Opportunity or Cause for Concern? Simon D. Roger and Ashraf Mikhail, J Pharm Pharmaceut Sci (www. cspsCanada.org) 10 (3): 405-410, 2007.

[16] Commentary, Biosimilars: it's not as simple as cost alone. S. D. Roger, MD FRACP and D. Goldsmith_ MA FRCP, Journal of Clinical Pharmacy and Therapeutics (2008) 33, 459–464.

[17] Biosimilars: How similar or dissimilar are they? Simon D Roger, Nephrology 2006; 11, 341–346.

[18] US-FDA: Biosimilar Development, Review, and Approval. https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval Assessed on 16 August 2019.

[19] TGA-Australia, Evaluation of biosimilars, https://www.tga.gov.au/sites/default/files/pm-argpm-biosimilars-150420_1.pdf Assessed on 16 August 2019.

[20] About Biosimilar manufacturing, https://www.biosimilardevelopment.com/solution/biosimilar-manufacturing, Assessed on 17 August 2019.