Global Status of Biosimilars and Its Influential Factors

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Abstract — The history of biosimilars started at European Union (EU) in 2006 with one product; however, currently it has been recognized everywhere in the world and EU have highest 64 biosimilar products. United States Food & Drug Administration (USFDA) was little unadventurous with biosimilars; nevertheless, they approved the first biosimilar 09 years after EU approval and presently they have 28 biosimilars which are playing significant role in price cutting of branded biologics. They also have so many biosimilars in product pipeline. Economically emerging countries especially China & India are very aggressive with biosimilars. In view of easy regulation, cheap labor & other cost related factors they are in little advantageous than the rivalries. Under Pharmaceutical Benefits Scheme Australian government is encouraging biosimilars and they already approved 20 biosimilars. Japan, Korea, Canada, South Africa are also promoting biosimilars. However, it is worth mentioning that in spite of enormous potentiality and rapid growth till to date biosimilar market is insignificant compared to total pharmaceutical market and success of biosimilars will depend on the acceptance by the physicians, treatment cost reduction, trust on manufacturer, proper information, drug substitution, efficacy, safety etc.

Index Terms — Biosimilars, follow on biologics, branded biologic, USFDA, price-cut, regulation, rapid growth, acceptance, potential, substitution, treatment cost, drug substitution, efficacy and safety.

I. INTRODUCTION

By 2020 almost 28% of the worldwide pharmaceutical market will be shared by biological products [1]. In last five years huge number of biological products have approved all over the world and almost 600 products are in pipeline [2]. Usually biological products are expensive than that of chemical products that leads to huge increment of total treatment cost [3]. Apart from the above many biotech products are going to off patented soon. Also, health spending as a percentage of GDP (Gross Domestic Products) is decreasing or almost static in many developed countries like United Kingdom (UK), Spain, Italy etc. and increasing in several emerging countries like India, China, Russia, South Africa, Brazil, Turkey etc. [4].

Some developed countries have not been able to solve the problem of the increase costs of healthcare resulting from technological development, public expectations and particularly the rapidly increasing size of their elderly populations. Also, the people of various developing countries are still living in below poverty line with dysfunctional health care systems and extremely limited access to basic medical care [5].

The biosimilars market is up-warding exponentially with the industry forecast to be worth $25 billion by 2020 [6]. Hence, biosimilars are equally important for both developed & developing countries. Considering the above this study find out the present status of biosimilars across the world and some influential factors associated with its growth.

II. OBJECTIVES

The objective of this study is to present the current approval status and market potential of different biosimilars across the world including major pharmaceutical markets. Also, the study aims to narrate the major factors associated with the growth of biosimilar products.

III. METHODOLOGY

This is a qualitative and exploratory study. All the data are collected from secondary sources and the author mostly relied on different journals, reference books, articles and various reputed websites. All the information gathered were precisely referenced and compiled with the concern of providing a detailed understanding of biosimilars status.

IV. FINDINGS

A. Biosimilars in Europe

In the European Union (EU), a legal structure for approving biosimilars was established in 2003. This edifice reveals that biosimilars can only be approved centrally via the European Medicines Agency (EMA) and it will not be wise to approve nationally. EMA first developed guidelines for the approval of biosimilars via an abbreviated registration process during 2005 to 2006 and since then EMA has developed many universal and precise guidelines for biosimilars [7].

By January 2016, 19 biosimilars based on 08 originator products-including the world’s first monoclonal antibody biosimilar had been approved for use in Europe. In 2013, biosimilars were responsible for around a quarter of all sales of biologics for which EU patents had expired. The European involvement with biosimilars has exposed substantial cost savings for healthcare providers and patients, with no reports of untoward effects or unexpected adverse events with biosimilars in Europe till to date [8].

Some studies estimate that by 2020, overall savings in the European Union could range from $16 to $45.2 billion [9].

Till to date, EMA has endorsed the sanction of 64 biosimilars within the product classes of:
1) growth hormone (GH);
2) granulocyte colony-stimulating factor (GCSF);
3) erythropoiesis stimulating agent (ESA);
4) insulin;

Published on November 8, 2020.
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DOI: http://dx.doi.org/10.24018/ejbmre.2020.5.6.565
5) follicle-stimulating hormone (FSH);  
6) parathyroid hormone;  
7) tumor necrosis factor (TNF)-inhibitor; and  
8) monoclonal antibodies (MABs) [10].

B. Biosimilars in USA

The USFDA was authorized to approve biosimilars by the BPCI (The Biologics Price Competition and Innovation) Act passed by the US Congress on March 23, 2010 and has issued a draft guidance in early 2012 [11].

The biosimilars market in the United States (US) has got momentum after the introduction of Novartis’ Zarxio (Filgrastim-sndz) in September 2015. Zarxio, the first biosimilar to be approved in the US, was a noteworthy development resulting in auspicious emerging trends for the growth of global biosimilars market. Sandoz claims that the launch of biosimilar has led to the gradual attrition of the market share of Amgen’s Neupogen; as Amgen’s first quarter 2016 results Neupogen (filgrastim) sales decreased by 13% driven by the effect of intense market competition in the US [12].

The main three factors that suggests biosimilars penetration may eventually reach high level in the US market are the price of pharmaceutical (double compare to average price of the rest of the world), total amount of healthcare expenditure (18% of GDP) and new health legislation-2014 [13].

As the US region would contribute single-digit revenue share in overall biosimilar market by 2020. Recently the USFDA (United States Food and Drug Administration) has approved its second biosimilar product Inflectra (infliximab-dyyb) as a reproduction of Janssen Biotech’s drug Remicade (infliximab). Though, Inflectra (infliximab) has already approved to market in many countries such as Canada, Mexico, Australia and European regions, it is the first biosimilar monoclonal antibody (MABs) to be approved in the US. Such developments would expose new opportunities for pharmaceutical companies and drug developers in the global market [12, 14]. As of now the number of approved biosimilars by USFDA is 28 where the most recent one is Hulio (adalimumab) [15].

However, it is assessed that biosimilars will lead to a $44.2 billion reduction in spending on biologic drugs from 2014 to 2024, or about 4% of total biologic spending over the same period, with a range of $13 billion to $66 billion [16].

C. Biosimilars in Emerging Countries

China, India, Brazil and Russia, among others, already have top in the marketplace, but they are about to dive in and change everything. Each of the said markets is huge. Under current circumstances, parochial clinical trial requirements and an uneven regulatory playing field would force many outside companies to establish distinct divisions simply to develop biosimilars in China and many other countries. The future success of biosimilars is not dependent on the US and Europe alone. The need is greatest in Asia and this market will influence the worldwide condition and be the fastest to adopt biosimilars. Drivers for fast uptake include low clinical development cost, unconstrained product launches due to a different patent landscape, cheap workforce, less strict regulatory framework and therapy primarily chosen by physicians [17]. Biosimilars have progressively added traction over the past few years. Forecasts suggest that global sales could more than double to $15 billion by the 2020s, with an estimated $5 billion to $8 billion coming from emerging markets [18].

D. Biosimilars in India

India, with its well-known track record of evolution in the generic pharmaceutical industry, can potentially emerge as a strong international player in the biosimilar segment. The Indian biosimilar industry is anticipated to grow from $4 billion in 2015 to more than $70 billion by 2025. Currently, more than 50 biotherapeutics are approved in the country and more than half are biosimilars. Although India does not have strict regulations, it has a big potential for biosimilars. Most innovator biotherapeutics are unaffordable to the average patient in India, even though the price in the local market is usually lower than that in Western countries [19]. Till to date around 90 biosimilar products have been approved in India and, according to Generics and Biosimilars (GaBI's) list [20].

E. Biosimilars in China

Available data shows 40% of China’s $1.5bln recombinant biologic product sales come from similar biologics, which have enjoyed approximately 25%-30% Compound annual growth rate (CAGR) over the past decade. If the market remains to grow at 25% per year, the similar biologic market could grow to $2bn, around 20% of the global biosimilar market by 2015. There are numerous issues driving the domestic biosimilar market: Firstly, changes in disease pattern; shifting of infectious diseases to non-communicable diseases (NCDs). Secondly, significant price reductions compared to originator products encourage reimbursements. Thirdly, a window of opportunity has been involuntarily created by today’s biosimilar leaders. As the first wave of biologic originators did not file or adequately protect its IP (Intellectual Property) in China during the 1990s, a number of local companies took benefit of this window of opening [21]. In February 2019, National Drug Regulators in China approved the first ever biosimilar product referencing Rituxan, a monoclonal antibody. This biosimilar product, HLX01 (Hanlikang), was developed by Shanghai Henlius Biopharmaceutical (Henlius), and is indicated in the treatment of non-Hodgkin’s lymphoma. This approval signaled the beginning of the Biosimilar boom in China [22].

F. Biosimilars in Korea

According to the Korea Pharmaceutical Manufacturers Association (KPMA), the biosimilars market in South Korea grew to $130 million, nearly twice in size from its 2013 value. Six biosimilars have been approved in South Korea since 2012 and currently this number is 12 [23]. Currently the number South Korea is pointing to capture a big share of the $110bn of value that Citigroup expects to flow from innovator companies to biosimilars over the next decade. Biosimilars have higher barriers to entry than traditional generics because of the huge investment and risk involvement. Yet Celltrion, a promising name among bio overcame these hurdles to develop the first copy of Johnson & Johnson’s rheumatoid arthritis drug Remicade, the world’s third best-selling drug last year with sales of
$10bln. This was seen as a milestone not only because of its high value but also because it was the first of a more complex group of biologics called monoclonal antibodies (MAbs) to face biosimilar competition. The Celltrion version, known as Remsima or Inflectra, was launched in Europe in February and is now sold in 40 countries across the globe. But the biggest market by far—the USA—so far remains elusive. The US FDA (United States Food and Drug Administration) approved its first biosimilar earlier this year in a sign that America is finally opening to the category after years of lobbying against it from some big pharmaceuticals and biotech groups [24]. To date, the Ministry of Food and Drug Safety (MFDS) has approved 11 biosimilars within the product classes of HER2-inhibitor, insulin, tumour necrosis factor (TNF)-inhibitor and monoclonal antibody, for use in South Korea [25].

G. Biosimilars in South Africa

South African medicine market is very sophisticated. Generics make up more than 50% of the market. Biosimilars guidelines were released in 2010. There is a financial burden on the system overall and great pressure to utilize generics including biosimilars. There is a cost containment focus from the government and payer side and a quality focus from the physician and patient side. Companies will have to bring in a cost structure that is lower than what currently exists along with the highest quality and safety profiles of their biosimilars [1].

Indian Drug firm Cipla will invest around Rand 1.3 billion (over Rs 590 crore) to launch a manufacturing facility in South Africa for the production of biosimilars. The company’s “proposed biotech subsidiary in South Africa will invest just over R 1.3 billion into the country’s first state-of-the-art biotech manufacturing facility, for the production of biosimilars” [26]. South Africa’s Medicines Control Council (MCC) has approved the country’s first non-originator biological, filgrastim, from Teva Pharmaceutical Industries [27].

H. Biosimilars in Japan

Pharmaceutical market of Japan is the second most important market in the world after the United States with a sale of over $143 billion in 2014, representing 14% of the global pharmaceutical market. The biopharmaceutical market in Japan is of great import to the world. However, most of the products sold there are of foreign origin but manufactured locally under license [28].

In March 2009, guidelines for biosimilars, based on the European Union’s existing processes, were issued by the MH LW (Ministry of Health, Labour and Welfare). These guidelines deliberate biosimilar drugs to be those products that are equivalent and homogenous to the reference biological product in terms of efficacy, quality and safety [28].

The first biosimilar to take approval in Japan was Sandoz’s growth hormone treatment Somatropin BS (somatropin) in June 2009. Till to date, the PMDA (Pharmaceuticals and Medical Devices Agency) has permitted seven biosimilars within the product classes of human growth hormone (HGH), granulocyte colony-stimulating factor (GCSF), erythropoiesis stimulating agent (ESA), insulin and tumour necrosis factor (TNF)-inhibitor, for use in Japan [28]. The PMDA has approved 21 biosimilars, within the product classes of human growth hormone, granulocyte colony-stimulating factor, erythropoiesis stimulating agent, insulin, angiogenesis inhibitor and tumour necrosis factor [29].

I. Biosimilars in Australia

The Australian Government recognized the emerging role of biosimilar medicines and will play in providing treatment opportunities to Australians in upcoming years. They have launched an initiative aimed at improving awareness and confidence in biosimilar medicines amongst prescribers, pharmacists, and patients in Australia. It has allocated $20 million to this initiative over a three-year period [30]. In accordance with this approach, the Therapeutic Goods Administration (TGA) released its updated guidelines on biosimilars, specifically referring to a number of European Medicines Agency (EMA) guidelines providing standards for quality, non-clinical and clinical data requirements for biosimilarity. In particular, the pricing consequences of the listing of a biosimilar medicine on the PBS (Pharmaceutical Benefit Scheme) are now certain a 16% price drop (from the subsidized price the government pays the sponsor) will happen on reference brands following the first listing of a biosimilar medicine on the PBS. The PBS listing of Inflectra brings a total of 09 biosimilar medicines approved for use in Australia [31]. However, till to date, TGA has permitted 20 biosimilars within the therapeutic classes of human growth hormone (HGH), granulocyte colony-stimulating factor (GCSF), insulin, erythropoietin, follicle stimulating hormone (FSH), monoclonal antibody (MAbs) and tumour necrosis factor (TNF)-inhibitor, for use in Australia [32].

J. Biosimilars in Canada

In 2010, Health Canada delivered the “Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)”, whose objective was to provide guidance on how to gratify the data and regulatory requirements under the Food and Drugs Act and Regulations for the authorization of subsequent entry biologics (SEBs) in Canada [11]. The first biosimilar in Canada, Omnitrope (somatropine), was approved in 2009 and Health Canada endorsed Celltrion’s Remsima/Inflectra in 2014. Health Canada recently issued restructured draft subsequent entry biologics (SEB) guidance, which will likely be finalized in 2016. There are now multiple pending patent cases involving biosimilar products on the Federal Court of Canada’s docket, with many novel issues at stake. Canada’s provinces are finally figuring out how to capitalize on biosimilar competition within their formulations [33]. Thus far in 2020, Health Canada has approved seven biosimilars of six innovator products. This brings the total Health Canada approvals to 25 biosimilars of 12 innovator products [34].
K. Scope for biosimilars due to patent expiry

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<th>Indication</th>
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L. Issues Influencing the Emerge of Global Biosimilars Market

The ongoing sharp rise in healthcare expenditure is untenable and imposes a substantial financial burden on patients, potentially limiting access to many effective therapies. In view of that above and rise in health budget in emerging countries biosimilars are gaining huge attention [36]. More than hundred biosimilars have been approved globally. Almost 15 patented biologics will be expiring by the end of 2020; also, it is foreseeable that the global biosimilars market could reach $25-$35 billion by 2020 representing a CAGR of 62.1% [37].

The followings are the influential factors for the growth of the biosimilars.

a) Acceptance of biologic drugs is growing mostly for chronic diseases (diabetes, arthritis and heart diseases) which are difficult to treat with small-molecule drugs

b) Customers & pharmacy benefit managers are continuing to progress their coverage strategies

c) Finalizing the Biosimilars interchangeability guidelines by USFDA.

d) Opportunity for biosimilars to be available at all distribution channels including full-line, wholesale distribution [38].

e) Numerous blockbuster biologics—Humira, Remicade and Lantus are going to lose patent protection over the next five to 10 years. It is worth mentioning that they are high valued and mostly prescribed biologics globally.

f) Specialist doctors, patients at the middle of biosimilars potential as prescription & usage rates are linked to Return on Investment models

g) Lucrative price advantages influence the governments in different countries to incentivize to use biosimilars

h) Clutter of global giants making in Europe and emerging markets

i) Drug delivery device firms knock the sweet spot

j) The healthcare industry is becoming biased to urban areas [39].

k) Advanced prevalence of cancer and existence of stringent regulatory have enabled North America & Europe to emerge dominant in the global Oncology biosimilars market

l) Asia-Pacific is scheduled to emerge as a strong regional market, mainly owing to the growing populations and healthcare awareness in India and China [40].

V. CONCLUSIONS

Changes in disease pattern, increasing number of aged populations, sedentary lifestyle and intensifying apprehension of the side effects of chemical molecules are triggering the growth of biological products; however, they are highly expensive everywhere in the world. Due to health cost reduction in many developed countries and increasing health budget in some developing countries including emerging economies biosimilars are gaining high level of attention for both rich and poor across the world. Also, patent expiry of some high valued biotech products and regulatory relaxation are pushing the rise of biosimilars. Europe, USA, Japan, Canada and Australia are the top places for pharmaceutical market and they very rich with biologic products. Their recent inclined towards biosimilars has offered a paradigm shift in the booming of biosimilars. Therefore, it is estimated that biosimilar market will enjoy an exponential growth in the upcoming years which will be far higher than chemical pharmaceutical products. Although some developed & developing countries have finalized their biosimilar guidelines, but many others are yet to publish it and there is some discrepancy among the published guidelines. Beyond doubt biosimilars are growing fast but acceptance by the physician, legal issues, technological soundness, reduction of total treatment cost, legal harmonization etc. need to be considered for the upcoming days of biosimilars

ACKNOWLEDGEMENT

The author would like to acknowledge all the individual writers, researchers, authorities, and organizations from where information was gathered to accomplish this paper. The author is also grateful to Dr. Syed Ferhat Anwar, Professor & Director, Institute of Business Administration (IBA), University of Dhaka for his kind guidance and support. It would be incomplete if the author does not mention the contribution of his family members and currently working company to write this article.
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